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(54) 1,4-Substituted piperidines as acetylcholinesterase inhibitors and their use for the treatment of Alzheimer's disease

1,4-Substituierte Piperidine als Acetylcholinesterase Inhibitoren und ihre Verwendung zur Behandlung von Alzheimer's Erkrankung

Pipéridines 1,4-substituées comme inhibiteurs de l'acétylcholinestérase et leur utilisation dans le traitement de la maladie d'Alzheimer

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EP 0 296 560 B1

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Description

The invention relates to a cyclic amine compound, a therapeutical composition and medical treatment of senile dementia.

(Statement of Prior Arts)

With a rapid increase in the population of aged people, the establishment of the therapy for senile dementia, such as Alzheimer senile dementia, is eagerly desired.

Various attempts have been made to treat the senile dementia with a drug. So far, however, there has been no drug which is very useful for the treatment of these diseases.

Studies on the development of therapeutic agents for these diseases have been made from various aspects. Particularly, since Alzheimer senile dementia is accompanied by the lowering in cholinergic hypofunction, the development of the therapeutic agent from the aspect of an acetylcholine precursor and an acetylcholinesterase inhibitor was proposed and is in fact attempted. Representative examples of the anticholinesterase inhibitor include physostigmine and tetrahydroaminoacridine. However, these drugs have drawbacks such as an unsatisfactory effect and the occurrence of unfavorable side effects. At the present time, there are no decisive therapeutic agents.

In view of the above situation, the present inventors have made extensive and intensive studies on various compounds for many years with a view to developing a drug which has a persistent activity and a high safety.

As a result, the present inventors have found that a piperidine derivative represented by the following general formula (XXV) and other specific piperidine derivatives can attain the desired object.

Specifically, the compound of the present invention represented by the following general formula (XXV) and other specific piperidine derivatives have great advantages of having strong and highly selective antiacetylcholinesterase activity, increasing the amount of acetylcholine present in the brain, exhibiting an excellent effect on a model with respect to disturbance of memory, and having a persistent activity and a high safety when compared with physostigmine which is a conventional popular drug in the art, which renders the compound of the present invention very valuable.

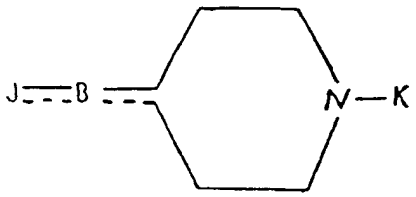
The compound of the present invention was found based on the acetylcholinesterase inhibitory action and, therefore, is effective for treatment and prevention of various diseases which are thought to be derived from the deficiency of acetylcholine as a neurotransmitter in vivo.

Examples of such diseases include various kinds of dementia including Alzheimer senile dementia and further include Huntington's chorea, Pick's disease, and ataxia.

Therefore, the objects of the present invention are to provide a novel piperidine derivative effective as a pharmaceutical, particularly for treatment and prevention of central nervous system diseases, to provide a process for preparing the same, and to provide a pharmaceutical comprising the same as an effective ingredient.

(Summary of the Invention)

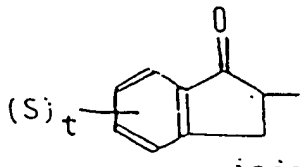
The invention provides a cyclic amine compound having the following formula (XXV) and a pharmacologically acceptable salt thereof:



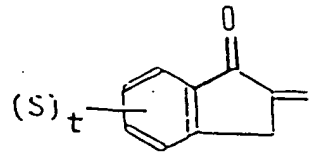
(XXV)

wherein:

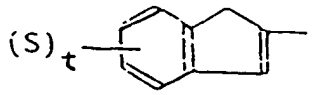
J is selected from:



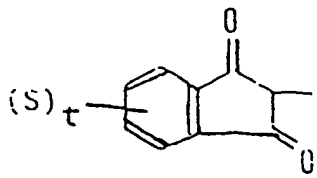
indanonyl



indanolidenyl



indenyl



indanedionyl

wherein S is a lower alkyl group having 1-6 carbon atoms, a lower alkoxy group having 1-6 carbon atoms, a halogen atom, a hydroxyl group, and t is 0-4, or $(S)_t$ may form a methylene dioxy group or an ethylene dioxy group on two adjacent carbon atoms of the phenyl group to which $(S)_t$ is attached;

B is one of the divalent groups $-(CHR^{22})_r-$, in which r is an integer from 0 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group; $=(CH-CH=CH)_b-$, in which b is an integer from 1 to 3; $=CH-(CH_2)_c-$, in which c is an integer from 0 to 9; or $=(CH-CH)_d=$, in which d is an integer from 0 to 5; and

K is a phenylalkyl group optionally substituted by a C_{1-6}alkyl group which may optionally be halogenated, a C_{1-6}alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6}alkoxycarbonyl group, an amino group, a C_{1-6}monoalkylamino group, a C_{1-6}dialkylamino group, a carbamoyl group, a C_{1-6}acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6}alkylaminocarbonyl group, a C_{1-6}alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6}alkoxy-C_{1-6}alkyl group; and

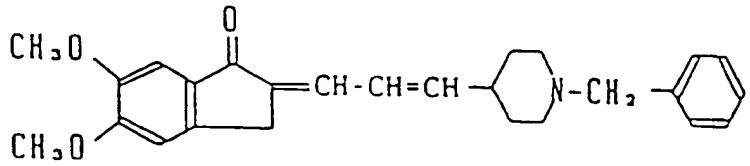
⎓ shows a single or a double bond.

Preferably, B is $-(CHR^{22})_r-$; R^{22} is a hydrogen atom; and r is an integer of 1 to 10.

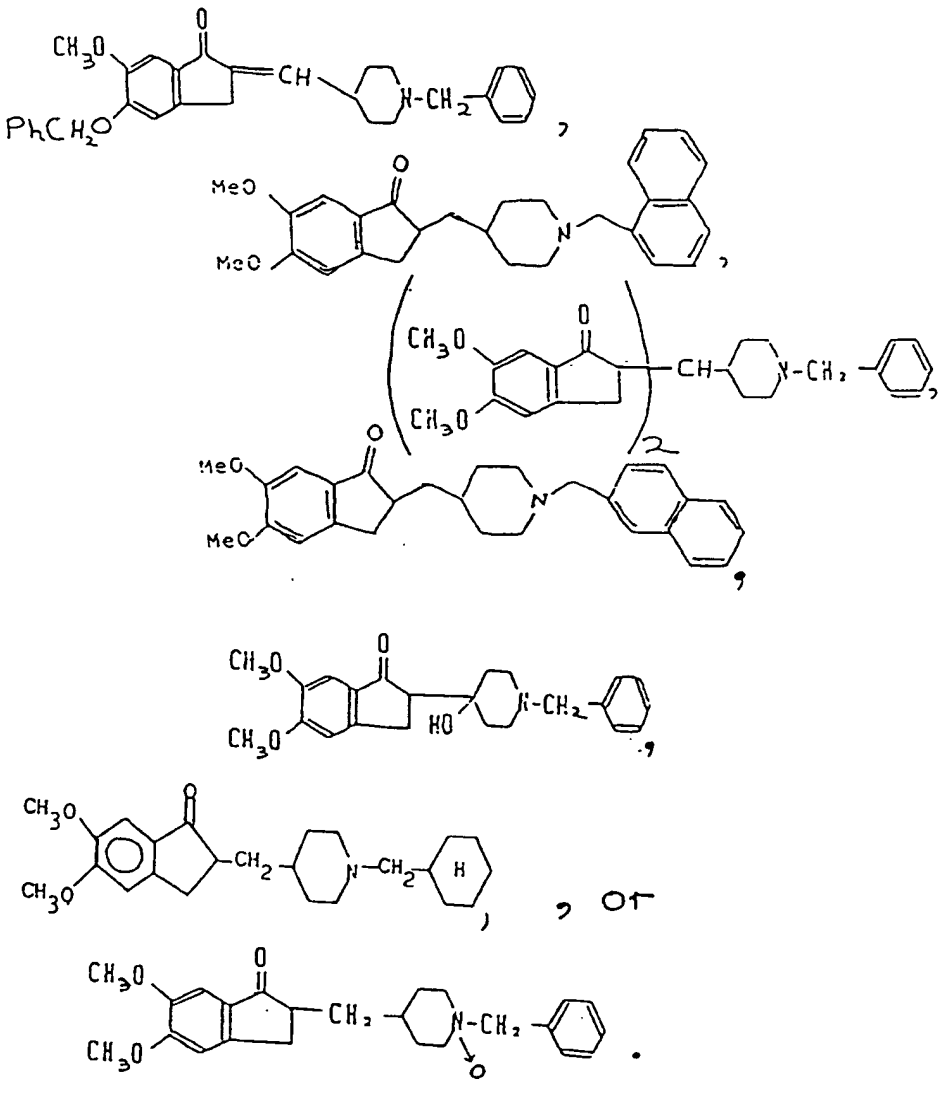
Preferable compounds of the invention include:

1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine,
1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-methylenedioxy-1-indanon)-2-yl)methylpiperidine,
1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,

1-(m-florobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,
1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine,
1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine and
1-benzyl-4-((5,6-dimethoxy-1-indanolidenyl-2-yl)propenylpiperidine, having the below shown formula, shown in Example 224.



The present invention also provides the following cyclic amine compounds or a pharmacologically acceptable salt thereof:



In addition, the invention provides a therapeutical composition which comprises a pharmacologically effective amount of the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier and then a method for preventing and treating a disease due to the acetylcho-

linesterase activity by administering to a human patient the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof. Among the substituents represented by S, methoxy is most preferable. t is preferably an integer of 1 to 4. The phenyl is most preferred to have 1 to 3 methoxy groups thereon.

In the definition B, $-(CHR^{22})_r-$ and $=CH-(CH_2)_c-$ are preferable.

In the present invention, the term "pharmacologically acceptable salt" include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide, and phosphate, and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate, and toluenesulfonate. Further, when a certain kind of substituent is selected, the compound of the present invention may form, e.g., alkali metal salts such as a sodium or potassium salt, alkaline earth metal salts such as a calcium or magnesium salt, organic amine salts such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, or N,N'-dibenzylethylenediamine.

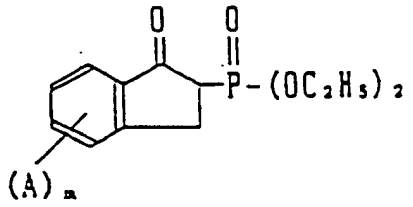
Moreover, the compounds of the present invention may have an asymmetric carbon atom depending upon the kind of the substituent and, therefore, have stereoisomers. They are, of course, within the scope of the present invention.

One specific example thereof will now be described. When J has an indanone skeleton, the compound of the present invention has an asymmetric carbon atom and, therefore, may have stereoisomers, optical isomers, diastereomers, etc. All of these isomers are within the scope of the present invention.

The compound of the present invention may be prepared by various processes. Representative processes for preparing the compound of the present invention will now be described.

Process B

When J in the general formula (XXV) is a monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl group and B is a group represented by the formula $-(CH_2)_n-$, wherein n is an integer of 1 to 6, the compound of the present invention can be prepared by the following process:



(VII)

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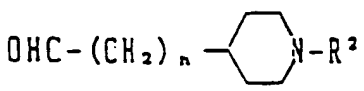
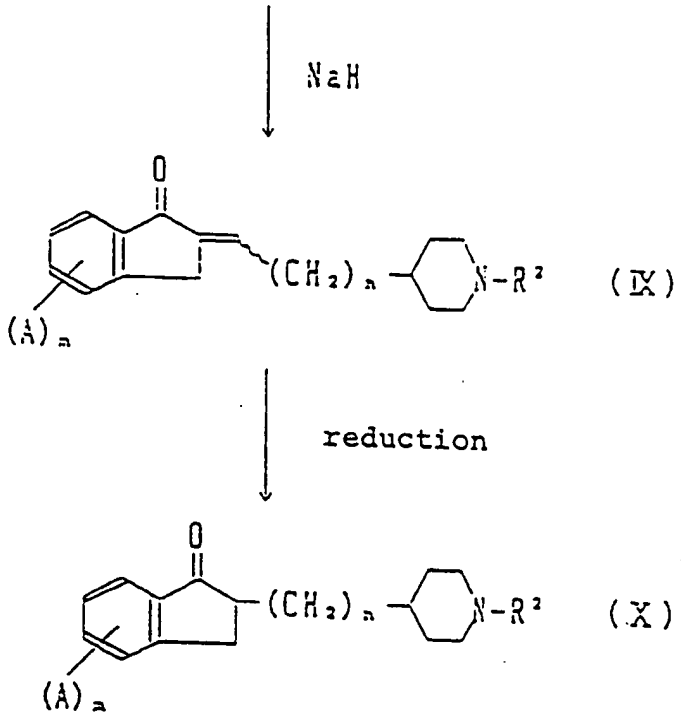


(VIII)

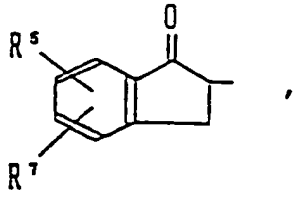


Specifically, a compound (X) which is one of the object compounds can be prepared by reacting a substituted 1-indanon-2-ylphosphonate represented by the general formula (VII) with an aldehyde compound represented by the formula (VIII) (i.e., Wittig reaction) to prepare a compound (IX) which is one of the object compounds and then catalytically reducing said compound (IX).

Examples of the catalyst used in the Wittig reaction include sodium methylate (MeONa), sodium ethylate (EtONa), tert-BuOK, and NaH. Examples of the solvent used in this reaction include tetrahydrofuran (THF), dimethylformamide (DMF), ether, nitromethane, and dimethyl sufoxide (DMSO). A reaction temperature ranging from room temperature to about 100°C provides favorable results.

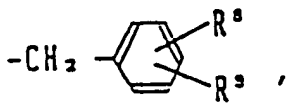
A catalytic reduction in the presence of a catalyst composed of palladium-carbon etc. provides favorable results.

The following scheme specifically shows a process for preparing the compound of the present invention, wherein J is a group represented by the formula



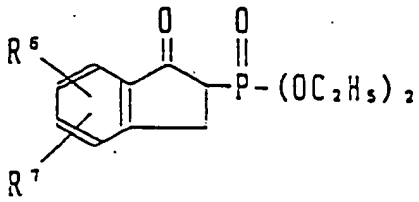
,

wherein R^6 and R^7 may be the same or different and are each a hydrogen atom, a lower alkyl group, a lower alkylalkoxy group, or a halogen atom among the groups defined by A, B is a group represented by the formula $-(CH_2)_n-$, wherein n is an integer of 1 to 6, K is a group represented by the formula



,

wherein R^8 and R^9 each have the same meaning as that of R^6 and R^7:



(VII)'

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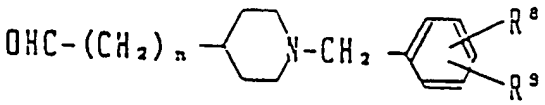
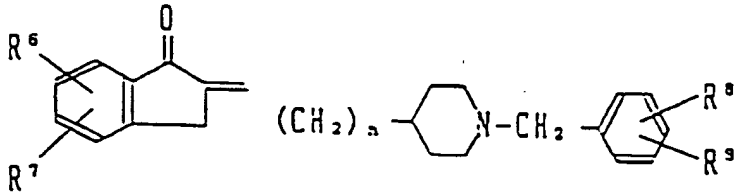
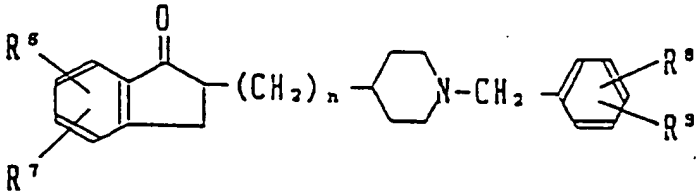


(VIII)'



(IX)'

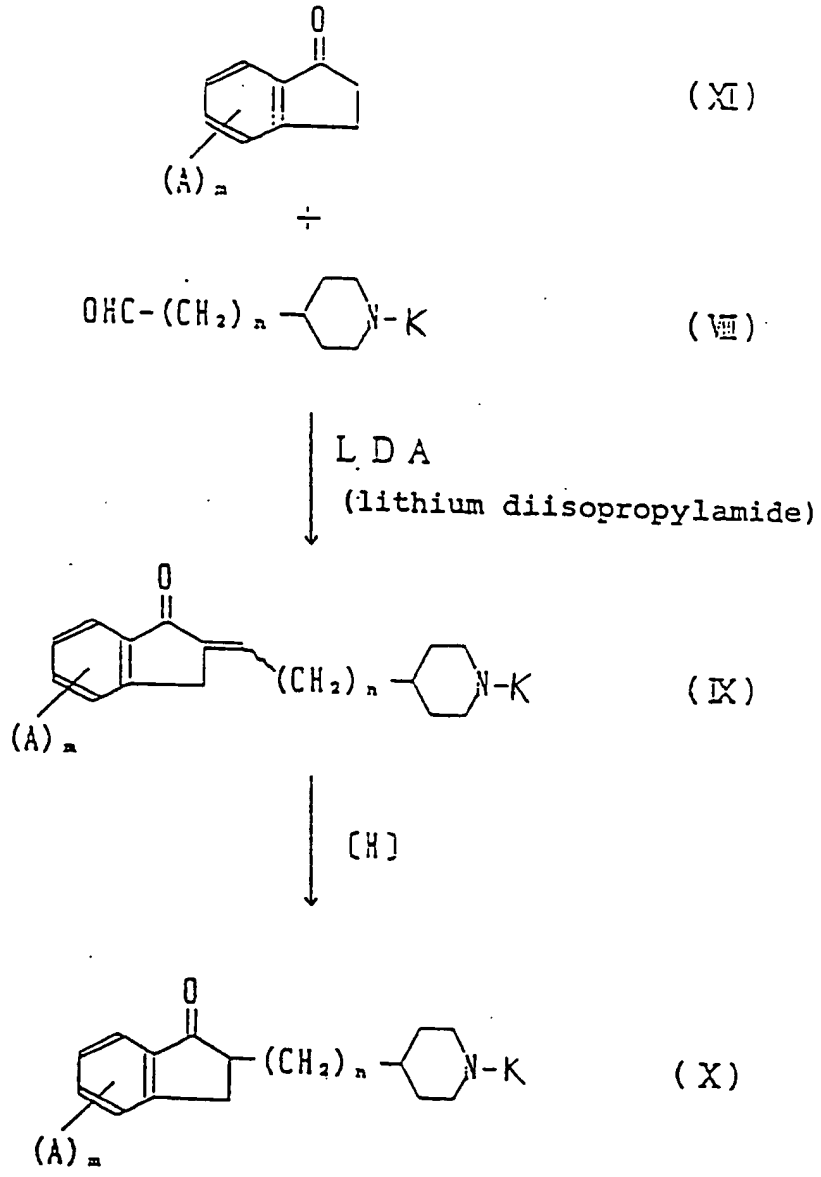


(X)'

Process C

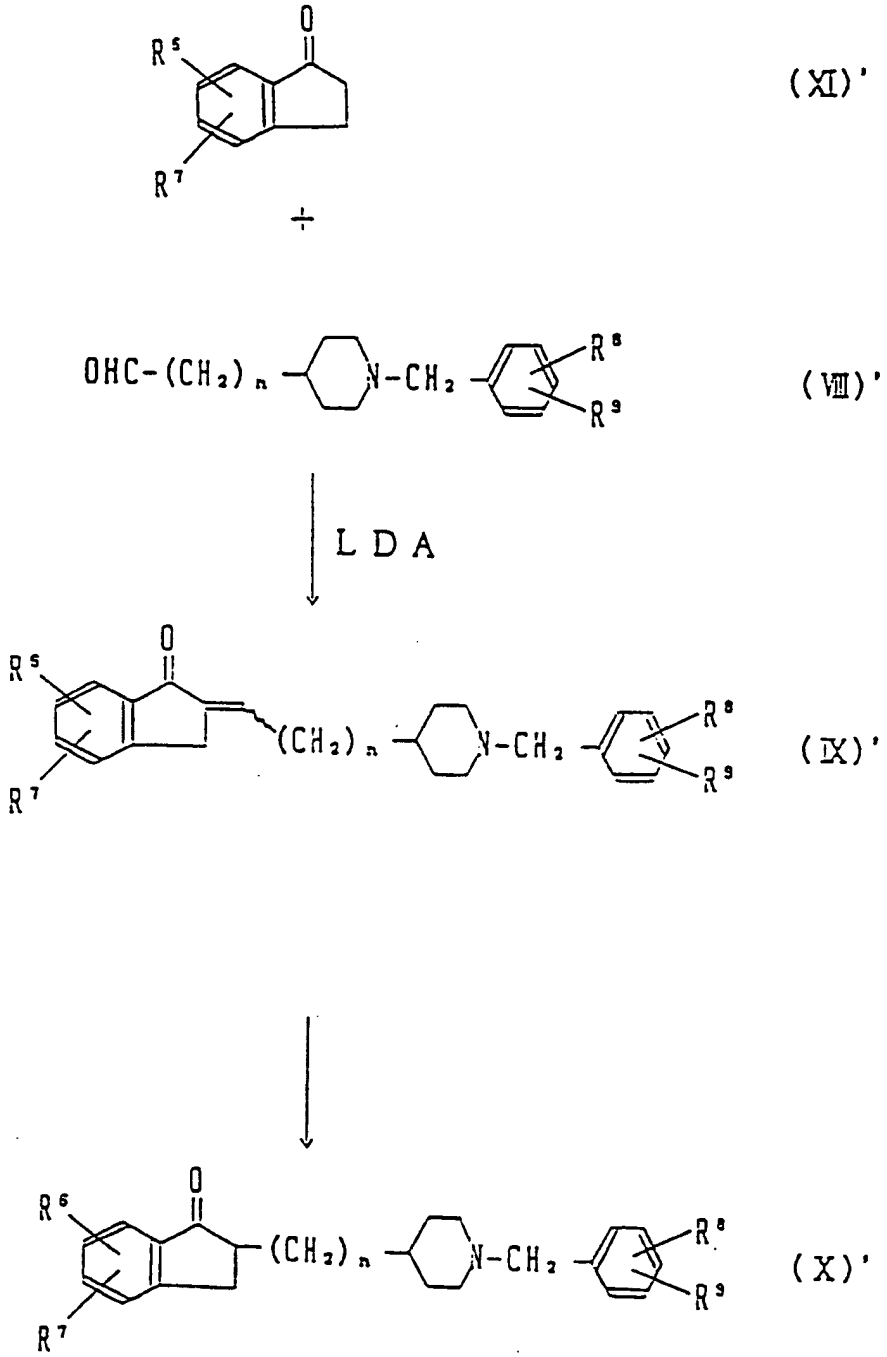
When J in the general formula (XXV) is a monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl group and B is a group represented by the formula $-(CH_2)_n-$, wherein n is an integer of 1

to 6, the compound of the present invention can be prepared also by the following process:



Specifically, for example, diisopropylamine and n-butyllithium/hexane are added to a solvent such as tetrahydrofuran. A substituted 1-indanone represented by the general formula (XI) and hexamethylphosphoric amide are added thereto at a temperature of preferably about -80°C. Then an aldehyde compound represented by the general formula (VIII) are added thereto, followed by a reaction according to an ordinary method. The reaction mixture is subjected to dehydration, thereby preparing a compound (IX). This compound may be catalytically reduced in the same manner as that of the Process B to prepare a compound (X).

A specific example of the Process C will now be described in the same manner as that described in the Process B.

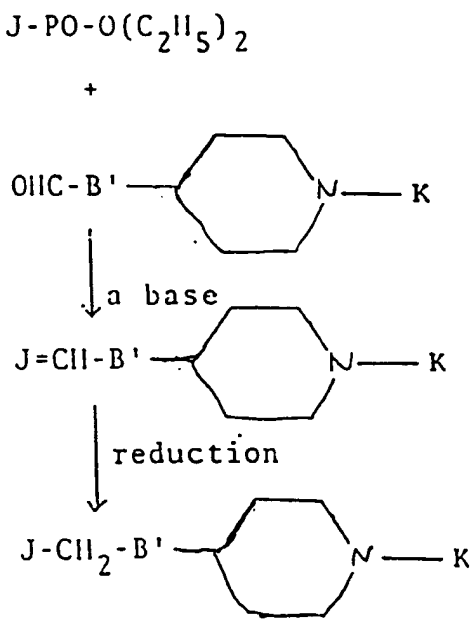


Process I

procedure 1

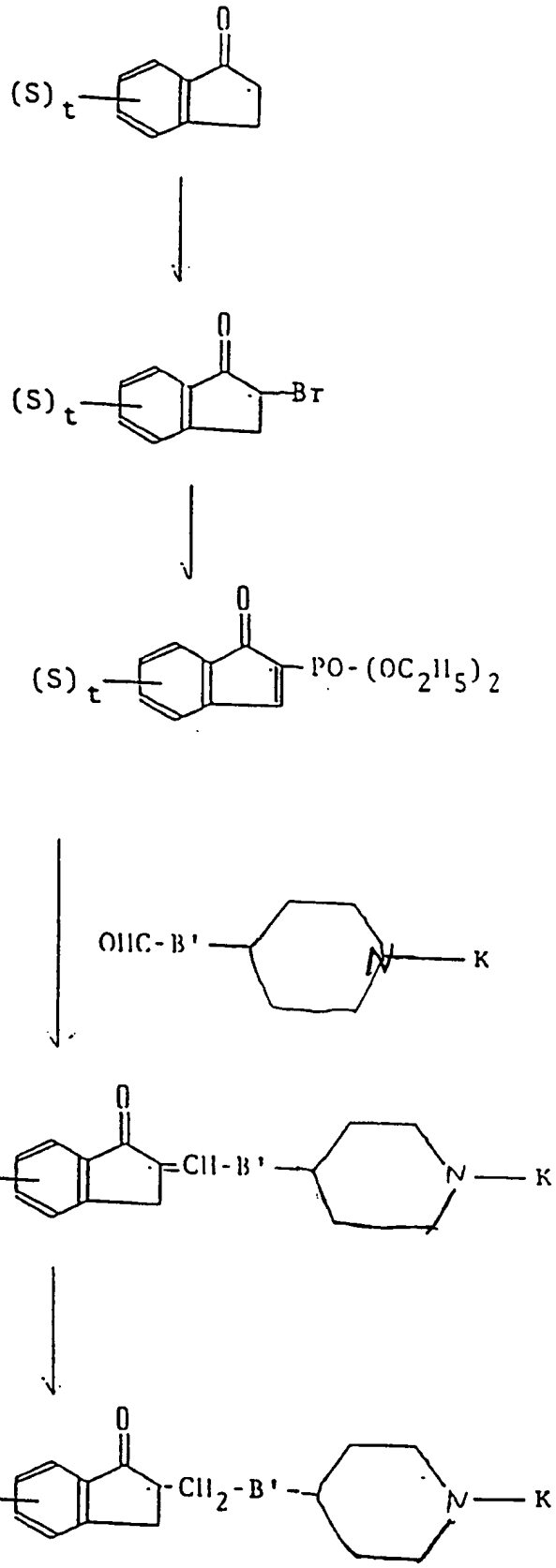
The cyclic amine compound having the formula (XXV) in which J is, (2) indanonyl, (5) indanedionyl, and B is -$(CHR^{22})_r$-, =(CH-CH=CH)$_b$-, =CH-$(CH_2)_c$- or =(CH-CH)$_d$= can be produced by the following procedure. B' is a group where

the terminal group containing one carbon atom is excluded from B.



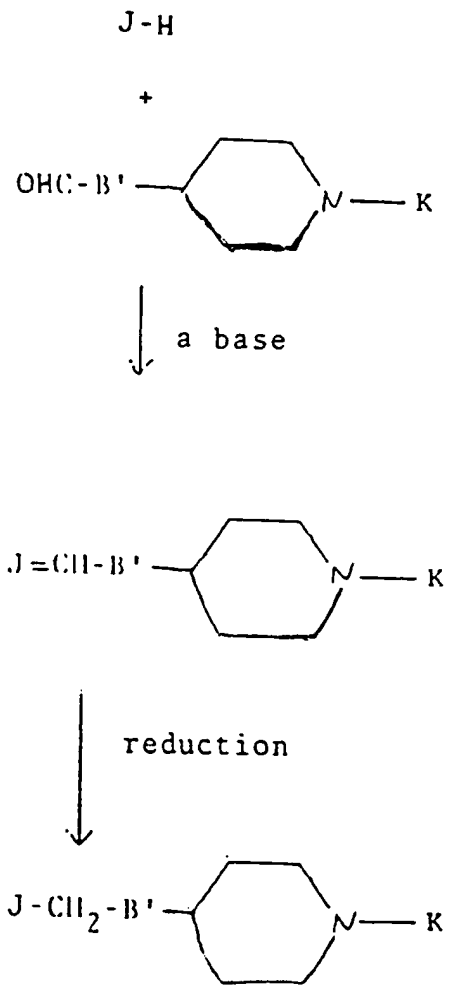
In this procedure, the phosphate is reacted with an aldehyde compound through the Wittig reaction and the product is catalytically reduced. The catalyst to use in the Wittig reaction, includes sodium methylate, sodium ethylate, potassium t-butyrate or sodium hydride. The reaction may be carried out in a solvent such as tetrahydrofurane, dimethylformamide, ether, nitromethane and dimethylsulfoxide at a temperature of the room temperature to 100°c. In the catalytical reduction, it is preferable to use a catalyst such as a catalyst of palladium and carbon, Raney nickel and a catalyst of rhodium and carbon.

In the above shown procedure, one example in which J is indanonyl goes:


(S)t
Br
PO-(OC2H5)2
OHC-B'
K
CH-B'
CH2-B'

procedure 2

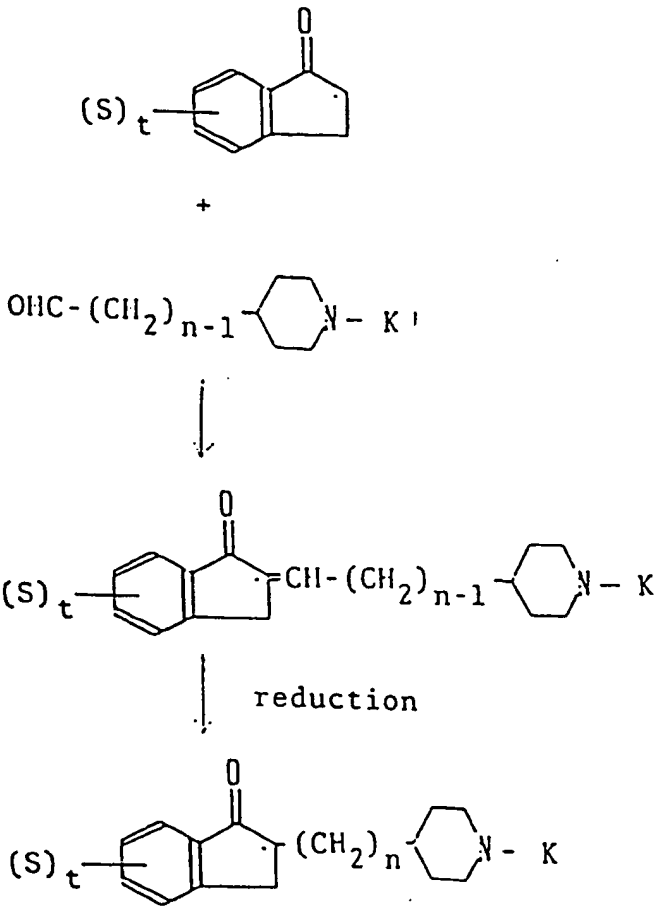
The compound as defined in the procedure 1 can be obtained also in the following way.



The compound of J-H such as indanone is reacted with an aldehyde by the conventional Aldole condensation to obtain an intended compound. The reaction may be carried out in a solvent such as tetrahydrofurane by first producing lithium di-isopropylamide from di-isopropylamine and a n-butylhexane solution of of lithium, adding thereto a compound of J-H at a temperature of preferably about minus 80°c, then adding the aldehyde thereto, effecting the reaction in the conventional way, heating the production mixture up to the room temperature to conduct dehydration and obtain the enone body of the intended compound. In another manner, the two reactants are dissolved in a solvent such as tetrahydrofurane, a base such as sodium methylate is added to the solution at about 0°c and the reaction is effected at the room temperature.

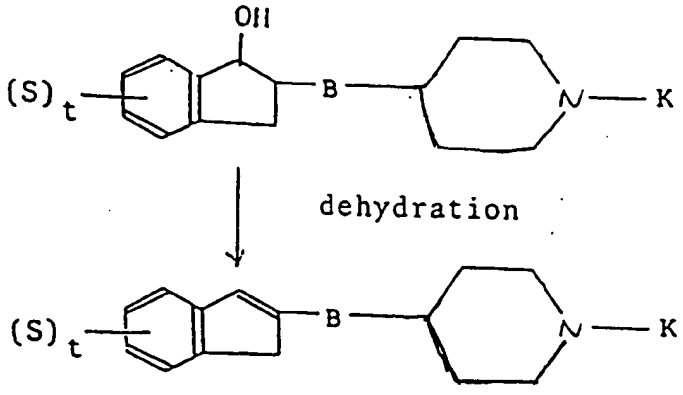
The enone body obtained this way can be reduced to obtain the intended compound.

One example in which J is indanonyl and B is -(CH_2)r-goes:



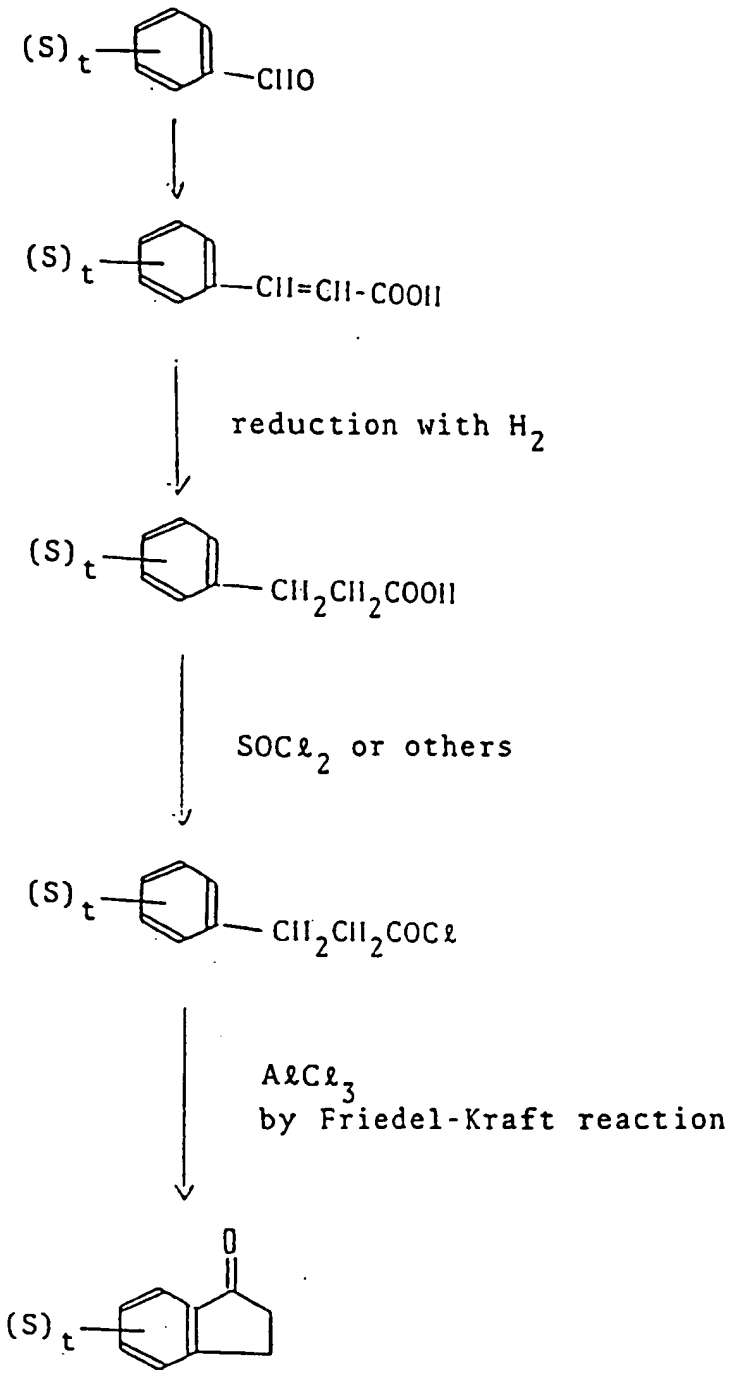
Process K

The compound having indenyl is produced by the following procedure. This procedure applies to the compound having indenyl having a substituent(s) on the phenyl.

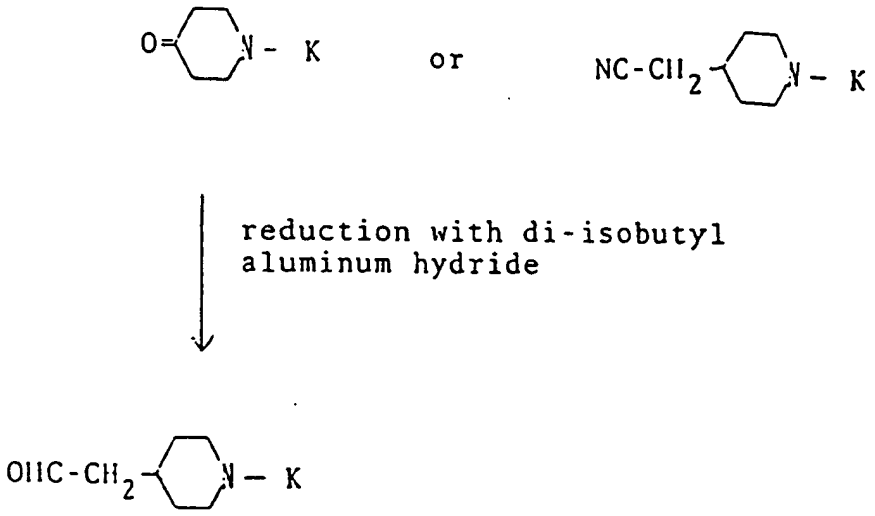


The dehydration is effected conventionally, for example, with hydrochloric acid.

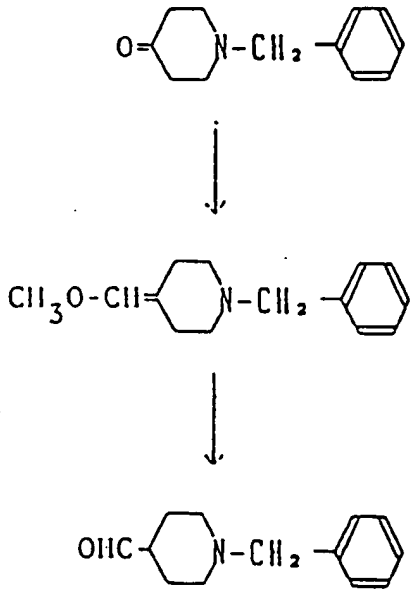
The indanone compound, as used in the above shown processes I and K, is available in the commmercial market and is produced by the following procedures.



The aldenyde compound used above is produced by the following procedures.

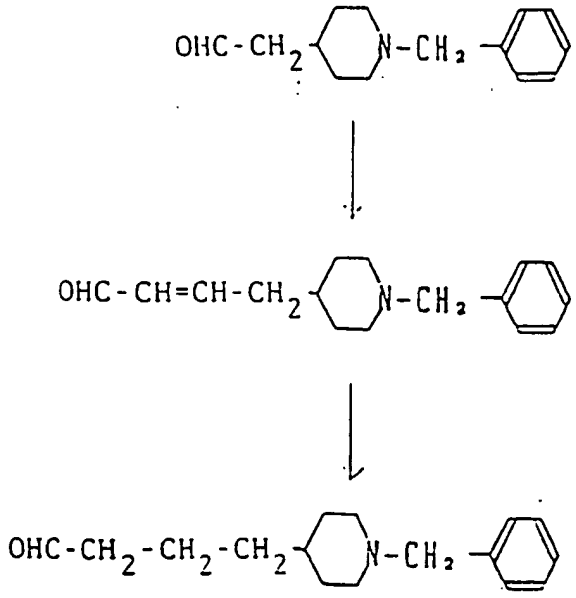


The above shown starting compound is converted to its aldehyde and the aldehyde is used for the Wittig reaction to increase the carbon number contained therein. The Wittig reaction is effected repeatedly or combined with another kind of the Wittig reaction. This is obvious to a man skilled in the art. The Wittig agent includes methoxymethylenetriphenylphosphorane to add one carbon atom and formylmethylenetriphenylphosphorane to add two carbon atoms. Methoxymethylenetriphenylphosphorane is obtained by the reaction between methoxymethylenetriphenylphosphonium chloride and n-butyl lithium in ether or tetrahydrofurane. Then a ketone compound or an aldehyde compound is added to the product mixture to obtain its methoxyvinyl compound and the resulting mixture is treated with an acid to obtain a corresponding aldehyde. One example goes:



When formylmethylenetriphenylphosphorane is used, a solution of a starting ketone or aldehyde in ether, tetrahydrofurane or bezene is mixed with this Wittig agent and the mixture is heated for reflux to obtain an intended compound.

The obtained unsaturated aldehyde compound may be converted to its saturated compound by the catalytic reduction using a catalyst of palladium and carbon, Raney nickel or a catalyst of rhodium and carbon. One example goes:



The compounds thus prepared and acid addition salts thereof represented by the general formula (XXV) are useful for treatment of various kinds of senile dementia, in particular senile dementia of the Alzheimer type.

The invention will be described in view of its therapeutical usefulness together with pharmacologically experimental data.

Experimental Example 1

In vitro acetylcholinesterase inhibitory action

A mouse brain homogenate was used as an acetylcholinesterase source and the esterase activity thereof was determined according to the method of Ellman et al.

Ellman, G.L., Courtney, K.D., Andres, V., and Featherstone, R.M., (1961) Biochem. Pharmacol., 7, 88-95.

Acetylthiocholine as a substrate, a sample to detect and DTNB were added to the mouse brain homogenate, followed by incubation. The amount of a yellow substance formed by the reaction between the thiocholine and DTNB was determined in the absorbance at 412 nm in terms of the acetylcholinesterase activity.

The acetylcholinesterase inhibitory activity of the sample was expressed in terms of inhibitory concentration 50% (IC_{50}).

The results are shown in Table 1.

Table 1

Compd. No.	AChE inhibitory activity IC_{50} (uM)
1	0.23
4	0.0053
29	0.15
31	0.025
33	0.030

Experimental Example 2

Ex vivo acetylcholinesterase inhibitory action

A sample to detect was orally administered to rats. After one hour of the administration, the cerebral hemispheres were dissected and homogenized, followed by the determination of the acetylcholinesterase activity. The group of rats treated with physiological saline was used as the control. Inhibition of AChE by samples ex vivo was expressed in terms of inhibition percent of the control value. Results are shown in Table 2.

Experimental Example 3

Action on passive avoidance learning impairment induced by scopolamine

See Z.Bokolanecky & Jarvik:Int.J.Neuropharmacol, 6, 217-222(1967).

Male Wister rats were used as the test animal and a step-through light and dark box was used as an apparatus. A sample to detect was orally administered one hour before the training and the rats were treated with 0.5 mg/kg (i.p.) of scopolamine 30 min. before the training. In a training experiment, the animal was placed into a light room and, just after the animal had entered into a dark room, a guillotine door was closed, followed by delivery of an electric shock from the gid of the floor. After six hours, the animal was again placed into a light room for a retention experiment, and the time taken for the animal to enter the dark room was measured for evaluation of the effect of the sample.

The difference in the response time between the physiological saline administration group and the scopolamine administration group was taken as 100%, and the effect of the sample was expressed in terms of the percentage antagonism by the sample (Reverse %).

The results are shown in Table 3.

Table 2

Compd. No.	Dose (mg/kg)	AChE inhibitory action (%)
Saline		0
4	1	5 *
	3	17 **
	10	36 **
	30	47 **

Table 3

Compd. No.	Dose (mg/kg)	Reverse %
4	0.125	55
	0.25	36

The number of animals per dose was 10 to 17.

NE:non-effective

The above-described pharmacological experiments revealed that the compound of the present invention had a potent acetylcholinesterase inhibitory action.

Among the compounds (I) of the present invention, the compound wherein J is an indanonyl or an idanolidenyl group derived from an indanone having an unsubstituted or substituted phenyl ring is preferable, and the compound wherein J is an indanonyl group is the most preferable. Specifically, particularly a compound wherein J is a group derived from an indanone having an unsubstituted or substituted phenyl ring has characteristics such as remarkable difference from the conventional acetylcholinesterase inhibitor in the structure, advantages with respect to the manufacture of pharmaceutical preparations by virtue of the potent acetylcholinesterase inhibitory action, large width between the main and the side effects, persistent activity, high water solubility, excellent stability, advantage in formulating into preparations, high bioavailability and excellent penetration into the brain.

Therefore, the objects of the present invention are to provide a novel compound effective for various kinds of dementia and the sequelae of cerebrovascular diseases, to provide a process for preparing the same, and to provide a novel pharmaceutical comprising the same as an effective ingredient.

A representative compound of the present invention (Compd. No. 4 in the above Table 3) was applied to toxicity tests on rats. As a result, the compound exhibited a toxicity of 100 mg/kg or more, i.e., exhibited no serious toxicity.

The compound of the present invention is effective for treatment, prevention, remission, improvement, etc. of various kinds of senile dementia, particularly senile dementia of the Alzheimer type; cerebrovascular diseases accompanying cerebral apoplexy, e.g. cerebral hemorrhage or cerebral infarcts, cerebral arteriosclerosis, head injury, etc.; and aprosexia, disturbance of speech, hypobulia, emotional changes, recent memory disturbance, hallucinatory-paranoid syndrome, behavioral changes, etc. accompanying encephalitis, cerebral palsy, etc.

Further, the compound of the present invention has a strong and highly selective anticholinesterase action, which renders the compound of the present invention useful also as a pharmaceutical based on this kind of action.

Specifically, the compound of the present invention is effective for, for example, Huntington's chorea, Pick's disease and delayed ataxia or tardive dyskiaesia other than senile dementia of the Alzheimer type.

When the compound of the present invention is used as a pharmaceutical for these diseases, it may be orally or parenterally administered. In general, it is parenterally administered in the form of injections, such as intravenous, subcutaneous, and intramuscular injections, suppositories, or sublingual tablets. The does will remarkably vary depending upon the symptom; age, sex, weight, and sensitivity of patients; method of administration; time and intervals of administration and properties, dispensing, and kind of pharmaceutical preparations; kind of effective ingredients, etc., so that there is no particular limitation with respect to the dose. Normally the compound may be administered in a dose of about 0.1 to 300 mg, preferably 1 to 100 mg, per day per adult, ordinarily in one to four portions.

Pharmaceutical preparations in the dosage form of, e.g., injections, suppositories, sublingual tablets, tablets, and capsules are prepared according to a method which is commonly accepted in the art.

In preparing injections, the effective ingredient is blended, if necessary, with a pH modifier, a buffer, a suspending agent, a solubilizing agent, a stabilizer, a tonicity agent, a preservative, etc., followed by preparation of an intravenous, subcutaneous, or intramuscular injection according to an ordinary method. In this case, if necessary, it is possible to lyophilize these preparations according to an ordinary method.

Examples of the suspending agents include methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, and polyoxyethylene sorbitan monolaurate.

Examples of the solubilizing agent include polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, and an ethyl ester of castor oil fatty acid.

Examples of the stabilizer include sodium sulfite, sodium metasulfite, and ether, and examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, and chlorocresol.

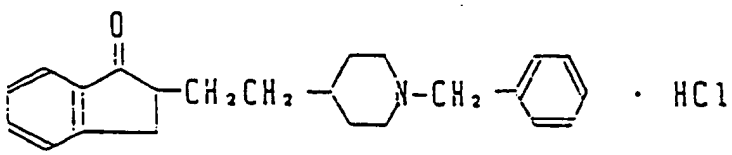
[Examples]

The present invention will now be described in more detail with reference to the following Examples. It is needless to say that the technical scope of the invention of the present invention is not limited to these Examples only.

In the following examples, all of the NMR values are those of the compounds measured in free form.

Example 1

1-Benzyl-4-[2-[(1-indanon)-2-yl]]ethylpiperidine hydrochloride



0.37 g of 1-benzyl-4-[2-[(1-indanon)-2-yl]]ethylpiperidine was dissolved in 10 ml of methanol, followed by addition of 0.1 g of 5% rhodium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 24 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride : methanol = 200 : 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting

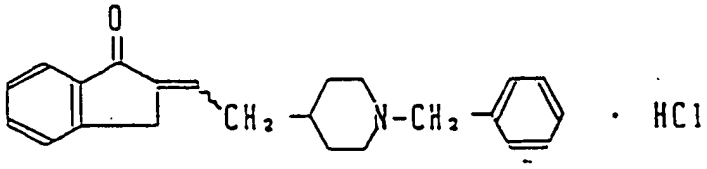
solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.33 g (yield: 80%) of the title compound having the following properties:

- m.p. (°C): 224-225°C
- elementary analysis: $C_{23}H_{27}NO \cdot HCl$

	C	H	N
calculated (%)	74.68	7.63	3.79
found (%)	74.66	7.65	3.77

Example 2

1-Benzyl-4-[2-[(1-indanon)-2-ylidenyl]]ethylpiperidine hydrochloride

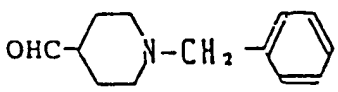


0.32 g of 60% sodium hydride was washed with hexane, and 10 mℓ of THF was added thereto. A solution of 2.12 g of diethyl 1-indanon-2-ylphosphonate in 30 mℓ of THF was dropwise added thereto at 0°C. The mixture was stirred at room temperature for 30 min and again cooled to 0°C, followed by addition of a solution of 3.43 g of 1-benzyl-4-piperidineacetoaldehyde in 10 mℓ of DMF. The mixture was stirred at room temperature for 2 hr and at 50°C for 2 hr and then refluxed for 2 hr while heating the mixture. Methanol and 20% sulfuric acid were added at 0°C to the reaction mixture. 10 min after the addition, the reaction mixture was made basic with an aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride : methanol = 500 : 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain 0.78 g (yield: 27%) of the title compound. 1.37 g diethyl 1-indanon-2-ylphosphorate was also recovered.

- molecular formula; $C_{23}H_{25}NO \cdot HCl$
- ^1H-NMR($CDCl_3$) δ ; 1.10~2.13(7H, m), 2.26 (2H, t), 2.88(2H, bd), 3.48(2H, s), 6.72~7.07(2H, m), 7.30(5H, s), 7.10~8.00 (5H, m)

Example 3

1-benzyl-4-piperidine-carboaldehyde having the formula:



was prepared in the following way.

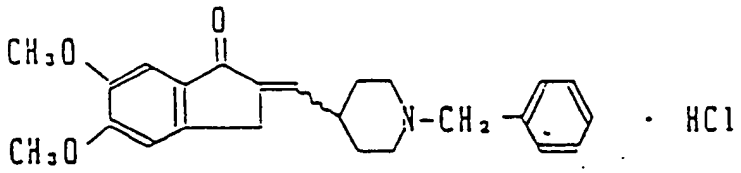
26 grams of methoxymethylene-triphenylphosphonium chloride was suspended in 200 ml of anhydrous ether. 1.6M solution in hexane of n-butyl lithium was added dropwise to the suspension at the room temperature. The mixture was stirred at the room temperature for 30 minutes and cooled down to 0°c. Then 30 ml of a solution in anhydrous ether of 14.35 g of 1-benzyl-4-piperidone was added to the mixture. It was stirred at the room temperature for 3 hours and filtrated to remove out the insoluble. The filtrate liquid was concentrated at a reduced pressure. The obtained concentrate was dissolved in ether and extracted with 1N hydrochloric acid. An aqueous solution of sodium hydroxide was added to the extract to have pH value of 12. The resultant was extracted with methylene chloride. The extract was dried with magne-

sium sulfate and concentrated at a reduced pressure. The residue was purified with a column filled with silica gel to obtain 5.50 g of an oil with a yield of 33 percent.

The oil was incorporated into 40 ml of methanol and 40 ml of 1N hydrochloric acid was added to the solution. It was heated so as to make reflux for 3 hours and then concentrated at a reduced pressure. The residue was dissolved in water. An aqueous solution of sodium hydroxide was added to the solution to have a pH value of 12 and the solution was extracted with methylene chloride. The extract was washed with saturated salt solution and dried with magnesium sulfate. It was further concentrated at a reduced pressure and the residue was purified in a column charged with silica gel. 2.77 g of the intended compound was obtained with a yield of 54 percent. In analysis, its molecular formula was found to be $C_{13}H_{17}NO$ and 1H-NMR ($CDC\ell_3$)δ , 1.40-2.40(7H,m), 2.78(2H, dt), 3.45(2H,S), 7.20(5H,S), 9.51(1H,d).

The compound may be produced according to the methods shown in (1) Arm. Kim. Zh., 36(9), 614-17 (1983) by R.A. Kuroyan, A.I. Markosyan, G.M. Snkhchyan and S.A. Vartangan and (2) Ind. Chim. Belge, 32, 64-5 (1967) by B. Hermans and P. Van Daele.

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine hydrochloride



This reaction was conducted in an argon atmosphere.

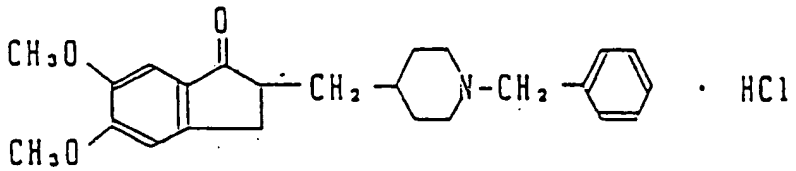
2.05 mℓ of diisopropylamine was added to 10 mℓ of anhydrous THF, followed by addition of 9.12 mℓ of a 1.6 M solution of n-butyllithium in hexane at 0°C. The mixture was stirred at 0°C for 10 min and then cooled to -78°C, and a solution of 2.55 g of 5,6-dimethoxy-1-indanone in 30 mℓ of anhydrous THF and 2.31 mℓ of hexamethyl-phosphoric amide were added thereto. The mixture was stirred at -78°C for 15 min, and a solution of 2.70 g of 1-benzyl-4-piperidine-carboaldehyde in 30 mℓ of anhydrous THF was added thereto. The temperature of the mixture was gradually raised to room temperature, followed by stirring for 2 hr. An aqueous 1% ammonium chloride solution was added thereto, and the organic phase was separated. The water phase was extracted with ethyl acetate, and the organic phases were combined with each other. The combined organic phase was washed with a saturated saline solution, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by making use of a silica gel column (methylene chloride : methanol = 500 : 1 - 100: 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 3.40 g (yield: 62%) of the title compound having the following properties:

- m.p. (°C): 237-238°C (dec.)
- elementary analysis: $C_{24}H_{27}NO_3 \cdot HCl$

	C	H	N
calculated (%)	69.64	6.82	3.38
found (%)	69.51	6.78	3.30

Example 4

1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride



0.4 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine was dissolved in 16 mℓ of THF, followed by addition of 0.04 g of 10% palladium-carbon. The mixture was hydrogenated at room temperature under atmospheric pressure for 6 hr. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by making use of a silica gel column (methylene chloride : methanol = 50 : 1). The eluate was concentrated in vacuo, and the residue was dissolved in methylene chloride. A 10% solution of hydrochloric acid in ethyl acetate was added to the resulting solution, followed by concentration in vacuo to obtain a crystal, which was recrystallized from methanol/IPE to obtain 0.36 g (yield: 82%) of the title compound having the following properties:

- m.p. (°C): 211-212°C (dec.)
- elementary analysis: $C_{24}H_{29}NO_3 \cdot HCl$

	C	H	N
calculated (%)	69.30	7.27	3.37
found (%)	69.33	7.15	3.22

Examples 28 to 41

The compounds synthesized in the same manner as that of Examples 1 to 4 are shown in Table 4.

Table 4

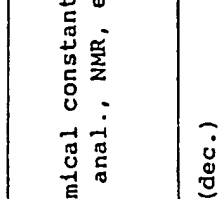
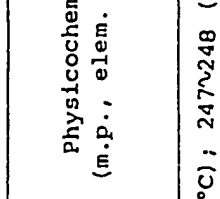
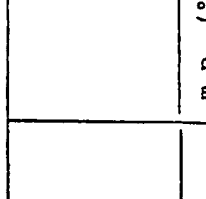
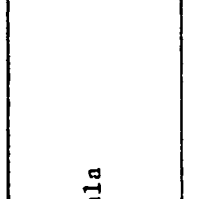
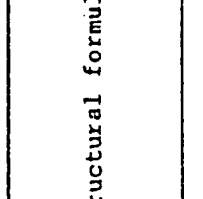
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
28		m.p. (°C); 247~248 (dec.) elem. anal.: $C_{23}H_{27}NO_3 \cdot HCl$ C H N calcd. (%) 68.73 7.02 3.48 found (%) 68.70 6.99 3.35
29		m.p. (°C); 196~197 elem. anal.: $C_{22}H_{25}NO \cdot HCl$ C H N calcd. (%) 74.24 7.36 3.94 found (%) 74.25 7.56 3.80
30		m.p. (°C); 203~204 (dec.) elem. anal.: $C_{23}H_{27}NO_2 \cdot HCl$ C H N calcd. (%) 71.58 7.31 3.63 found (%) 71.58 7.25 3.65
31		^{1}H-NMR(CDCl$_3$)δ; 1.10~3.40(14H,m),3.48(2H,s), 3.81(3H,s), 3.85(3H,s), 3.85(3H,s), 6.25(1H,bs), 6.42(1H,bs),7.25(5H,s) mol. form.; $C_{24}H_{29}NO_3 \cdot HCl$
32		^{1}H-NMR(CDCl$_3$)δ; 1.05~3.40(14H,m), 3.45(2H,s), 3.80(3H,s), 3.85(3H,s), 6.75(2H,ABq), 7.22(5H,s) mol. form.; $C_{24}H_{29}NO_3 \cdot HCl$

Table 4 (cont'd)

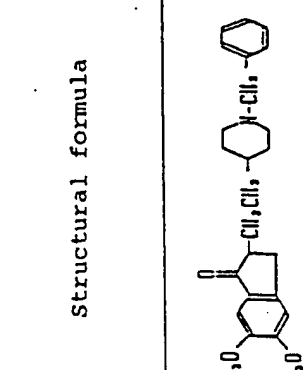
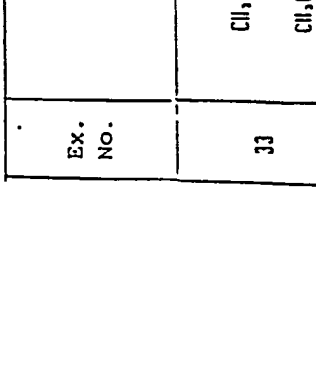
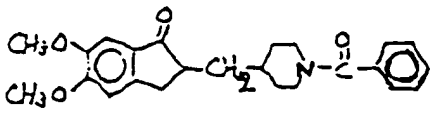
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
33		m.p. (°C); 201~202 (dec.) elem. anal.: $C_{25}H_{31}NO_3 \cdot HCl$ C H N calcd. (%) 69.83 7.50 3.26 found (%) 69.13 7.42 3.31 $1/5H_2O$ (%) 69.25 7.53 3.23 ^1H-NMR($CDCl_3$)δ; 1.10~3.40(11H,m), 3.50(2H,s), 3.05(3H,s), 3.93(3H,s), 4.25(1H,bs), 6.81(1H,s), 7.07(1H,s), 7.22(5H,s) mol. form.; $C_{23}H_{27}NO_4$
34		m.p. (°C); 225~226 (dec.) elem. anal.: $C_{23}H_{25}NO_3 \cdot HCl$ C H N calcd. (%) 69.08 6.55 3.50 found (%) 68.78 6.43 3.50
35		m.p. (°C); 169~170 (dec.) elem. anal.: $C_{22}H_{23}NO \cdot HCl$ C H N calcd. (%) 74.67 6.84 3.96 found (%) 74.42 6.61 3.76
36		m.p. (°C): 120~122 elem. anal.: $C_{23}H_{25}NO_2 \cdot HCl$ C H N calcd. (%) 71.96 6.83 3.65 found (%) 71.84 6.85 3.46
37		

Table 4 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
38		^{1}H-NMR($CDCl_3$)δ; 1.40~2.40(7H,m), 2.90(2H,bd), 3.48(2H,s), 3.51(2H,bd), 3.82(3H,s), 3.86(3H,s), 6.30(1H,bd), 6.43(1H,bd), 6.50(1H,bt), 7.23(5H,s) mol. form.; $C_{24}H_{27}NO_3 \cdot HCl$
39		^{1}H-NMR($CDCl_3$)δ; 1.40~2.50(7H,m), 2.86(2H,bd), 3.50(4H,s), 3.90(3H,s), 3.94(3H,s), 6.59(1H,dt), 6.78(2H,ABq), 7.22(5H,s) mol. form.; $C_{24}H_{27}NO_3 \cdot HCl$
41		^{1}H-NMR($CDCl_3$)δ; 1.10~2.32(9H,m), 2.90(2H,bd), 3.52(4H,s), 3.89(3H,s), 3.93(3H,s), 6.71(1H,tt), 6.84(1H,s), 7.20(1H,s), 7.24(5H,s) mol. form.; $C_{25}H_{29}NO_3 \cdot HCl$

Example 178

1-Benzoyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine



0.85 g of 5,6-dimethoxy-1-indanone and 1.38 g of 1-benzoyl-4-piperidinecarbaldehyde were dissolved in 20 ml of anhydrous THF to obtain a solution. 1.02 g of 28 % sodium methylate was added to the solution at 0°C. The obtained mixture was stirred at a room temperature for 2 hours; diluted with ethyl acetate, washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column to obtain 1.23 g of 1-benzoyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]methylpiperidine (yield : 71 %).

1.23 g of this compound was dissolved in 20 ml of THF, followed by the addition of 0.3 g of 10 % palladium/carbon. After the hydrogenation had been carried out at a room temperature under an ordinary pressure for one day, the catalyst was filtered out and the filtrate was concentrated in a vacuum. The residue was recrystallized from methylene chloride/hexane to obtain 1.10 g of the title compound (yield : 89 %). The characteristics thereof are as follows:

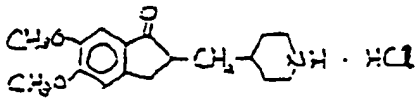
m.p. (°C) : 151 to 152

elemental analysis as $C_{24}H_{27}NO_4$

	C	H	N
calculated(%)	73.26	6.92	3.56
found(%)	73.30	6.85	3.32

Example 179

4-[(5,6-Dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride



9.00 g of 1-benzoyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine was dissolved in 90 ml of dioxane, followed by the addition of 90 ml of 6N hydrochloric acid. The obtained mixture was heated under reflux for 10 hours and concentrated in a vacuum. The residue was diluted with water and extracted with ethyl acetate. The pH of the aqueous layer was adjusted to 12 with a 50 % aqueous solution of sodium hydroxide and extracted with methylene chloride. The organic layer was washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was converted into its hydrochloride by an ordinary method. The obtained product was recrystallized from methanol/ethanol to obtain 6.30 g of the title compound (yield : 85 %). The characteristics thereof are as follows:

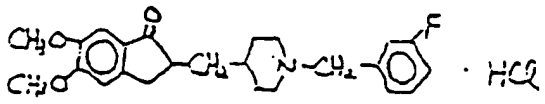
m.p. (°C): 249 to 250 (dec.)

elemental analysis as $C_{17}H_{23}NO_3 \cdot HCl$

	C	H	N
calculated(%)	62.67	7.42	4.30
found(%)	62.75	7.31	4.52

Example 180

1-(3-Fluorobenzyl)-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride



0.25 g of 4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine was dissolved in 6 ml of THF, followed by the addition of 0.29 ml of triethylamine and 0.13 ml of 3-fluorobenzyl bromide. The obtained mixture was heated under reflux for 2 hours and concentrated in a vacuum. The residue was diluted with ethyl acetate, washed with a 10 % aqueous solution or sodium carbonate and a saturated aqueous solution of common salt successively, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method. The obtained product was recrystallized from methylene chloride/IPE to obtain 0.27 g of the title compound (yield : 72 %). The characteristics thereof are as follows:

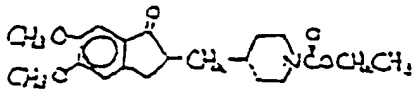
m.p. (°C): 230 to 232 (dec.)

elemental analysis as $C_{24}H_{28}NO_3 \cdot HCl$

	C	H	N
calculated(%)	66.43	6.74	3.23
found(%)	66.18	6.79	3.11

Example 182

4-[(5,6-Dimethoxy-1-indanon)-2-yl]methyl-1-ethoxycarbonylpiperidine



0.50 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine was dissolved in 8 ml of benzene, followed by the addition of 0.15 ml of ethyl chloroformate. The obtained mixture was heated under reflux for 3 hours, diluted with ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous soltuion of common salt successively, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was

recrystallized from ethyl acetate/hexane to obtain 0.45 g of the title compound (yield : 94 %). The characteristics thereof are as follows:

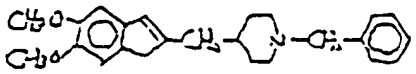
m.p. (°C): 132 to 133

elemental analysis as $C_{20}H_{27}NO_5$

	C	H	N
calculated(%)	66.46	7.53	3.88
found(%)	66.79	7.53	4.00

Example 185

1-Benzyl-4-[(5,6-dimethoxyinden)-2-yl]methylpiperidine hydrochloride



0.24 g of 1-benzyl-4-[(5,6-dimethoxy-1-indanol)-2-yl]methylpiperidine was dissolved in 5 ml of methylene chloride, followed by the addition of a 10 % solution of hydrochloric acid in ethyl acetate. The obtained mixture was concentrated in a vacuum. The obtained residue was recrystallized from methylene chloride/IPE to obtain 0.24 g of the title compound (yield : 95 %). The characteristics thereof are as follows:

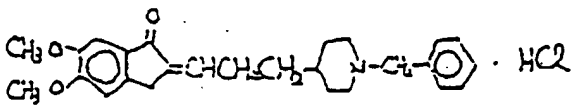
m.p. (°C): 216 to 217 (dec.)

elemental analysis as $C_{24}H_{29}NO_2 \cdot HCl$

	C	H	N
calculated(%)	72.07	7.56	3.50
found(%)	71.82	7.63	3.33

Example 186

1-Benzyl-4-[3-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]]propylpiperidine hydrochloride



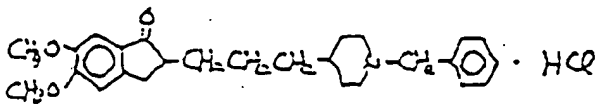
0.31 ml of diisopropylamine was added to 5 ml of anhydrous THF. 1.39 ml of a 1.6 M solution of n-butyllithium in hexane was further added to the obtained mixture at 0°C. The obtained mixture was stirred at 0°C for 10 minutes and cooled to -78°C, followed by the addition or a solution of 0.39 g of 5,6-dimethoxy-1-indanone in 5 ml of anhydrous THF and 0.35 ml of hexamethylphosphoramide. The obtained mixture was stirred at -78°C for 15 minutes, followed by the addition of a solution of 0.50 g of 3-(1-benzyl-4-piperidine)propionaldehyde in 5 ml of anhydrous THF. The obtained mixture was gradually heated to a room temperature, stirred at that temperature for 3 hours, diluted with ethyl acetate, washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and concentrated in a vacuum. The obtained residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method of obtain 0.55 g of the title compound as an oil (yield : 61 %).

molecular formula : $C_{26}H_{31}NO_3 \cdot HCl$

^{1}H-NMR($CDCl_3$) δ; 1.10~3.00(13H,m), 3.45(2H,S), 3.50(2H,S), 3.90(3H,S), 3.95(3H,S), 6.58~7.20 (3H,m), 7.27(5H,S).

Example 187

1-Benzyl-4-[3-[(5,6-dimethoxy-1-indanon)-2-yl]]propylpiperidine hydrochloride



0.40 g of 1-benzyl-4-[3-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]]propylpiperidine was dissolved in 15 ml of THF, followed by the addition of 0.1 g of 10 % palladium/carbon. After the hydrogenation had been carried out at a room temperature under an ordinary pressure for 2 hours, the catalyst was filtered out and the filtrate was concentrated in a vacuum. The residue was purified through a silica gel column and converted into its hydrochloride by an ordinary method to obtain 0.37 g of the title compound as an oil (yield : 84 %).

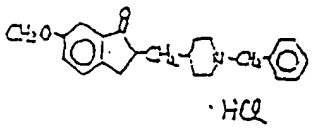
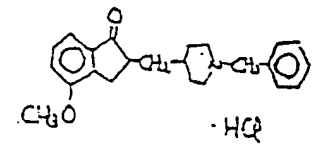
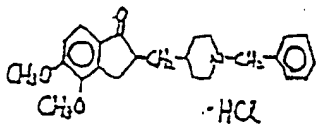
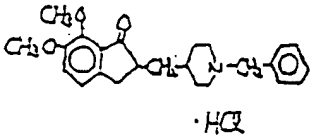
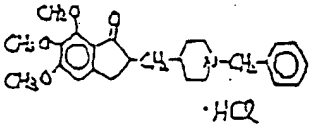
molecular formula: $C_{26}H_{33}NO_3 \cdot HCl$

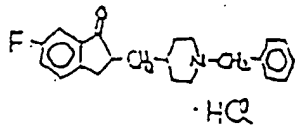
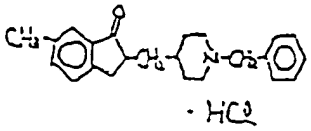
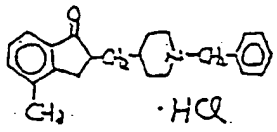
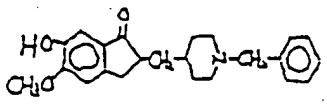
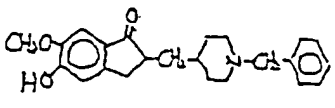
^{1}H-NMR($CDCl_3$) δ ; 1.00~3.30(18H, m), 3.38, 3.43 (total 2H, each S), 3.85(3H,S), 3.90(3H,S), 6.77, 6.83 (total 1H, each S), 7.05, 7.10 (total 1H, each S), 7.18, 7.20 (total 5H, each S).

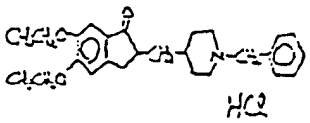
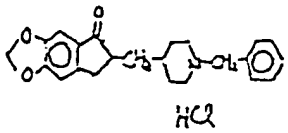
Examples 188 to 249

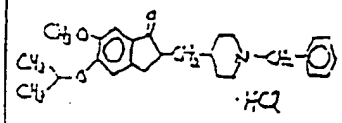
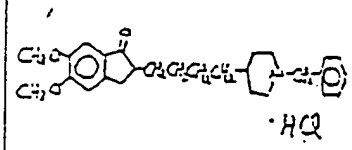
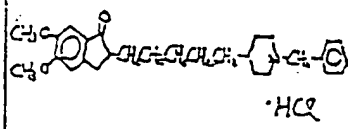
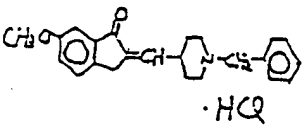
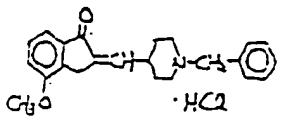
The compounds listed in Table 9 were each synthesized and analyzed.

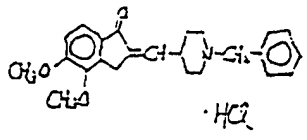
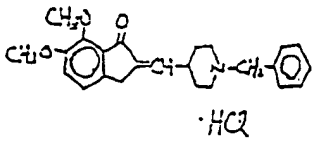
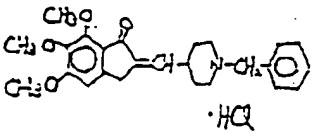
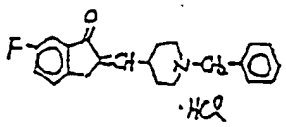
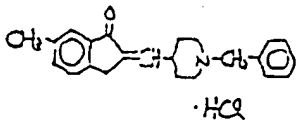
Table 9

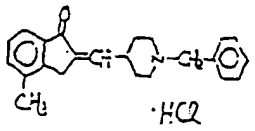
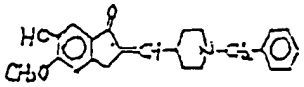
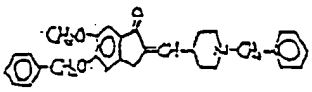
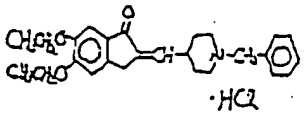
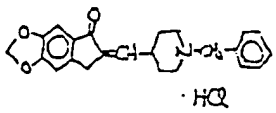
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
188		^{1}H-NMR($CDCl_3$) δ; 1.00∿3.40(14H,m), 3.47(2H,S), 3.78(3H,S), 6.90∿7.50(3H,m), 7.23(5H,S). molecular formula: $C_{23}H_{27}NO_2 \cdot HCl$
189		^{1}H-NMR($CDCl_3$) δ; 1.05∿2.12(9H,m), 2.50∿3.40(5H,m), 3.48(2H,S), 3.88(3H,S), 6.98(1H,q), 7.15∿7.32(2H,m), 7.23(5H,S), molecular formula: $C_{23}H_{27}NO_2 \cdot HCl$
190		m.p.(°C) : 199 to 200 (dec.) elemental analysis as $C_{24}H_{29}NO_3 \cdot HCl$ C H N calculated(%) 69.30 7.27 3.37 found(%) 69.24 7.40 3.38
191		m.p.(°C) : 198 to 199 elemental analysis as $C_{24}H_{29}NO_3 \cdot HCl$ C H N calculated(%) 69.30 7.27 3.37 found(%) 69.15 7.42 3.47
192		m.p.(°C) : 200 to 201 elemental analysis as $C_{25}H_{31}NO_4 \cdot HCl$ C H N calculated(%) 67.33 7.23 3.14 found(%) 67.10 7.16 3.00

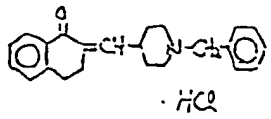
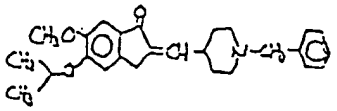
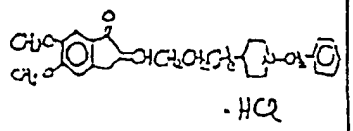
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
193		^{1}H-NMR($CDCl_3$) δ; 1.05∿2.15(9H,m), 2.55∿3.43(5H,m), 3.48(2H,S), 7.23(5H,S), 7.23∿7.43 (3H,m). molecular formula: $C_{22}H_{24}NOF \cdot HCl$
194		m.p.(°C): 175 to 177 elemental analysis as $C_{23}H_{27}NO \cdot HCl$ C: calculated(%) 74.68, found(%) 72.77, 1/2 H_2O (%) 72.90; H: 7.63, 7.64, 7.71; N: 3.79, 3.62, 3.70
195		m.p.(°C): 211 to 213 (dec.) elemental analysis as $C_{23}H_{27}NO \cdot HCl$ C: calculated(%) 74.68, found(%) 72.68, 1/2 H_2O (%) 72.90; H: 7.63, 7.49, 7.71; N: 3.79, 3.70, 3.70
196		m.p.(°C): 153 to 154 elemental analysis as $C_{23}H_{27}NO_3$ C: calculated(%) 75.59, found(%) 75.77; H: 7.45, 7.28; N: 3.83, 3.64
197		m.p.(°C): 170 to 171 (dec.) elemental analysis as $C_{23}H_{27}NO_3$ C: calculated(%) 75.59, found(%) 75.61; H: 7.45, 7.47; N: 3.83, 3.55

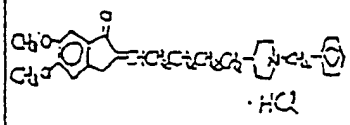
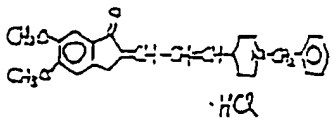
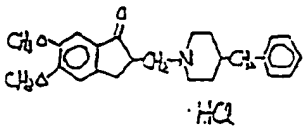
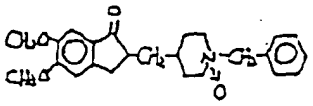
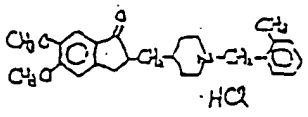
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
198		m.p.(°C): 175 to 176 elemental analysis as $C_{26}H_{33}NO_3 \cdot HCl$ C H N calculated(%) 70.33 7.72 3.15 found(%) 70.20 7.46 3.35
199		m.p.(°C): 236 to 237 (dec.) elemental analysis as $C_{23}H_{25}NO_3 \cdot HCl$ C H N calculated(%) 69.08 6.55 3.50 found(%) 68.97 6.82 3.29

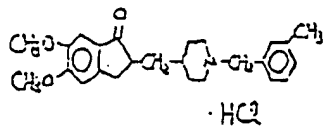
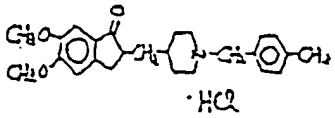
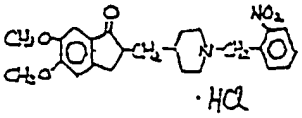
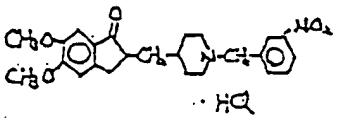
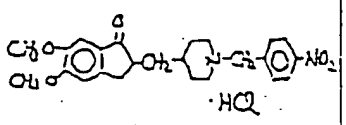
Example	Structural formula	Physicochemical constants (m.p., elemental analysis. NMR etc.)
203		m.p.(°C): 126 to 127 elemental analysis as $C_{26}H_{33}NO_3 \cdot HCl$ C H N calculated(%) 70.33 7.72 3.15 found(%) 70.41 7.48 2.85
204		^{1}H-NMR($CDCl_3$) δ; 1.00∿3.40(20H,m), 3.50(2H,S), 3.90(3H,S), 3.97(3H,S), 6.88(1H,S), 7.18(1H,S), 7.31(5H,S). molecular formula: $C_{27}H_{35}NO_3 \cdot HCl$
205		^{1}H-NMR($CDCl_3$) δ; 1.05∿3.36(22H,m), 3.45(2H,S), 3.85(3H,S), 3.90(3H,S), 6.78(1H,S), 7.08(1H,S), 7.21(5H,S). molecular formula: $C_{28}H_{37}NO_3 \cdot HCl$
206		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.50(7H,m), 2.70∿3.02(2H,m), 3.48(2H,S), 3.56(2H,S), 3.79(3H,S), 6.69(1H,dt), 7.02∿7.50(3H,m), 7.21(5H,m). molecular formula: $C_{23}H_{25}NO_2 \cdot HCl$
207		^{1}H-NMR($CDCl_3$) δ; 1.50∿3.57(11H,m), 3.48, 3.50(total 2H, each S), 3.83, 3.85 (total 3H, each S), 6.57∿7.39(4H,m), 7.22(5H,m). molecular formula: $C_{23}H_{25}NO_2 \cdot HCl$

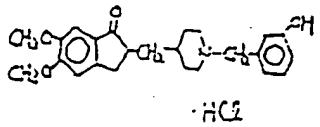
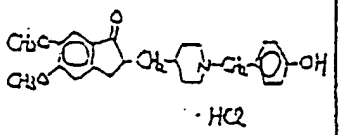
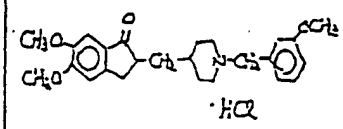
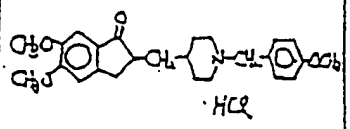
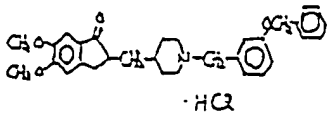
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
208		^{1}H-NMR($CDCl_3$) δ; 1.58∿2.55(7H,m), 2.79∿3.02(2H,m), 3.50(2H,S), 3.63(2H,d), 3.90 (6H,S), 6.63(1H,dt), 6.93(1H,d), 7.22(5H,S), 7.57(1H,d). molecular formula: $C_{24}H_{27}NO_3 \cdot HCl$
209		^{1}H-NMR($CDCl_3$) δ; 1.50∿2.55(7H,m), 2.78∿3.03(2H,m), 3.48(2H,S), 3.56(2H,d), 3.85(3H,S), 4.00(3H,S), 6.62(1H,dt), 7.07(1H,d), 7.21(1H,d), 7.22(5H,S). molecular formula: $C_{24}H_{27}NO_3 \cdot HCl$
210		^{1}H-NMR($CDCl_3$) δ; 1.50∿2.50(7H,m), 2.78∿3.03(2H,m), 3.48(2H,S), 3.53(2H,d), 3.82(3H,S), 3.90(3H,S), 4.03(3H,S), 6.58(1H,dt), 6.61(1H,S), 7.25(5H,S). molecular formula: $C_{25}H_{29}NO_4 \cdot HCl$
211		^{1}H-NMR($CDCl_3$) δ; 1.52∿2.55(7H,m), 2.78∿3.02(2H,m), 3.50(2H,S), 3.59(2H,S), 6.72(1H,dt), 7.05∿7.55(3H,m), 7.22(5H,S). molecular formula: $C_{22}H_{22}NOF \cdot HCl$
212		^{1}H-NMR($CDCl_3$) δ; 1.50∿2.55(7H,m), 2.38(3H,S), 2.78∿3.02(2H,m), 3.48(2H,S), 3.57(2H,S), 6.66(1H,dt), 7.38∿7.60 (3H,m), 7.21(5H,S). molecular formula: $C_{23}H_{25}NO \cdot HCl$

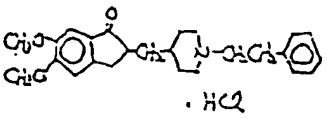
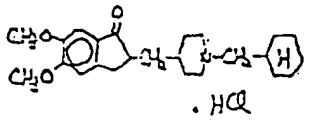
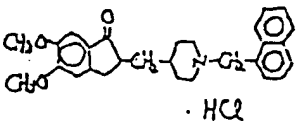
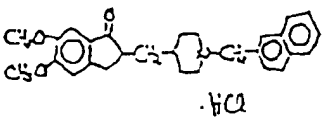
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
213		^{1}H-NMR($CDCl_3$) δ; 1.48∿2.60(7H,m), 2.32(3H,S), 2.77∿3.02(2H,m), 3,49(4H,S), 6.69(1H,dt), 7.10∿7.67(3H,m), 7.22(5H,S). molecular formula: $C_{23}H_{25}NO \cdot HCl$
214		m.p.(°C): 174 to 175 elemental analysis as $C_{23}H_{25}NO_3$ C H N calculated(%) 69.08 6.55 3.50 found(%) 69.12 6.41 3.43
215		m.p.(°C): 175 to 176 elemental analysis as $C_{30}H_{31}NO_3$ C H N calculated(%) 79.44 6.89 3.09 found(%) 79.04 6.87 2.77
216		m.p.(°C): 180 to 181 elemental analysis as $C_{26}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 70.65 7.30 3.17 found(%) 70.34 7.05 3.07
217		m.p.(°C): 228 to 230 (dec.) elemental analysis as $C_{23}H_{23}NO_3 \cdot HCl$ C H N calculated(%) 69.43 6.08 3.52 found(%) 67.89 5.97 3.45 1/2 H_2O (%) 67.89 6.19 3.44

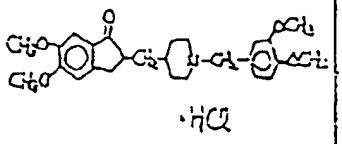
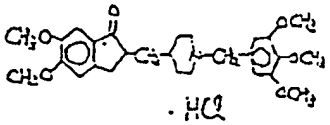
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
218		^{1}H-NMR($CDCl_3$) δ; 2.48∿3.02(13H,m), 3.48(2H,S), 6.73(1H,dt), 7.10∿8.10(4H,m), 7.22(5H,S). molecular formula: $C_{23}H_{25}NO \cdot HCl$
221		m.p.(°C): 170 to 171 elemental analysis as $C_{26}H_{31}NO_3$ C: calculated(%) 77.01, found(%) 77.10; H: calculated(%) 7.70, found(%) 7.67; N: calculated(%) 3.45, found(%) 3.43
222		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.40(13H,m), 2.70∿3.00(2H,m), 3.45(2H,S), 3.48(2H,S), 3.86(3H,S), 3.91(3H,S), 6.68(1H,tt), 6.80(1H,S), 7.20(6H,S). molecular formula: $C_{27}H_{33}NO_3 \cdot HCl$

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
223		^{1}H-NMR($CDCl_3$) δ; 1.10∿2.40(15H,m), 2.68∿3.00(2H,m), 3.46(2H,S), 3.50(2H,S), 3.88(3H,S), 3.93(3H,S), 6.68(1H,tt), 6.83(1H,S), 7.19(1H,S), 7.21(5H,S). molecular formula: $C_{28}H_{35}NO_3 \cdot HCl$
224		m.p.(°C): 130 to 135 elemental analysis as $C_{26}H_{29}NO_3 \cdot HCl$ C: calculated(%) 70.98, found(%) 70.81; H: calculated(%) 6.87, found(%) 6.72; N: calculated(%) 3.18, found(%) 3.10
225		^{1}H-NMR($CDCl_3$) δ; 1.10∿3.50(16H,m), 3.87(3H,S), 3.93(3H,S), 6.80(1H,S), 7.00∿7.25 (6H,m). molecular formula: $C_{24}H_{29}NO_3 \cdot HCl$
226		m.p.(°C): 186 to 188 (dec.) ^{1}H-NMR($CDCl_3$) δ; 1.65∿2.10(7H,m), 2.65∿2.75(2H,m), 3.25∿3.83(5H,m), 3.92(3H,S), 3.98(3H,S), 4.60(2H,S), 6.88(1H,S), 7.19(1H,S), 7.26∿7.60(5H,m). molecular formula: $C_{24}H_{29}NO_4$
227		m.p.(°C): 220 to 221 elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C: calculated(%) 69.83, found(%) 70.03; H: calculated(%) 7.50, found(%) 7.51; N: calculated(%) 3.26, found(%) 3.26

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
228		m.p.(°C): 212 to 213 elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C: calculated(%) 69.83, found(%) 69.62 H: calculated(%) 7.50, found(%) 7.38 N: calculated(%) 3.26, found(%) 3.15
229		m.p.(°C): 229 to 230 (dec.) elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C: calculated(%) 69.83, found(%) 69.91 H: calculated(%) 7.50, found(%) 7.48 N: calculated(%) 3.26, found(%) 3.28
230		^1H-NMR($CDCl_3$) δ; 1.00~3.50(14H,m), 3.73(2H,S), 3.86(3H,S), 3.93(3H,S), 6.82(1H,S), 7.12(1H,S), 7.22~7.80(4H,m). molecular formula: $C_{24}H_{28}N_2O_5 \cdot HCl$
231		m.p.(°C): 210 to 211 elemental analysis as $C_{24}H_{28}N_2O_5 \cdot HCl$ C: calculated(%) 62.54, found(%) 62.48 H: calculated(%) 6.34, found(%) 6.34 N: calculated(%) 6.08, found(%) 5.96
232		m.p.(°C): 234 to 236 (dec.) elemental analysis as $C_{24}H_{28}N_2O_5 \cdot HCl$ C: calculated(5) 62.54, found(%) 62.56 H: calculated(%) 6.34, found(%) 6.25 N: calculated(%) 6.08, found(%) 5.83

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
233		^{1}H-NMR($CDCl_3$) δ; 1.10∿3.43(14H,m), 3.52(2H,S), 3.84(3H,S), 3.91(3H,S), 6.35∿7.08 (7H,m). molecular formula: $C_{24}H_{29}NO_4 \cdot HCl$
234		m.p.(°C): 146 to 148 elemental analysis as $C_{24}H_{29}NO_4 \cdot HCl$ C: calculated(%) 66.51, found(%) 66.73; H: calculated(%) 7.29, found(%) 7.00; N: calculated(%) 3.53, found(%) 3.24
235		m.p.(°C): 193 to 194 elemental analysis as $C_{25}H_{31}NO_4 \cdot HCl$ C: calculated(%) 67.33, found(%) 67.43; H: calculated(%) 7.23, found(%) 7.22; N: calculated(%) 3.14, found(%) 3.13
236		m.p.(°C): 226 to 228 (dec.) elemental analysis as $C_{25}H_{31}NO_4 \cdot HCl$ C: calculated(%) 67.33, found(%) 67.21; H: calculated(%) 7.23, found(%) 7.29; N: calculated(%) 3.14, found(%) 2.97
237		^{1}H-NMR($CDCl_3$) δ; 0.78∿3.40(14H,m), 3.46(2H,S), 3.85(3H,S), 3.91(3H,S), 5.01(2H,S), 6.78(1H,S), 6.80∿7.43(9H,m), 7.09(1H,S). molecular formula: $C_{31}H_{35}NO_4 \cdot HCl$

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
239		m.p.(°C): 253 to 256 (dec.) elemental analysis as $C_{25}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 69.83 7.50 3.26 found(%) 69.60 7.49 3.27
240		m.p.(°C): 225 to 226 (dec.) elemental analysis as $C_{24}H_{35}NO_3 \cdot HCl$ C H O calculated(%) 68.31 8.60 3.32 found(%) 68.17 8.49 3.51
241		m.p.(°C): 226 to 227 (dec.) elemental analysis as $C_{28}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 72.17 6.92 3.01 found(%) 71.71 7.07 2.85
242		m.p.(°C): 243 to 245 (dec.) elemental analysis as $C_{28}H_{31}NO_3 \cdot HCl$ C H N calculated(%) 72.17 6.92 3.01 found(%) 71.75 6.92 3.01

Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
243		m.p.(°C): 191 to 192 elemental analysis as $C_{26}H_{33}NO_5 \cdot HCl$ C H N calculated(%) 65.60 7.20 2.94 found(%) 65.34 7.27 2.79
244		m.p.(°C): 219 to 221 elemental analysis as $C_{27}H_{35}NO_6 \cdot HCl$ C H N calculated(%) 64.09 7.17 2.77 found(%) 63.27 7.19 2.51 1/2 H_2O(%) 62.96 7.24 2.72

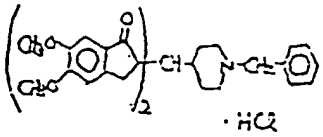
Example	Structural formula	Physicochemical constants (m.p., elemental analysis, NMR etc.)
249		m.p.(°C): 230 to 232 (dec.) elemental analysis as $C_{35}H_{39}NO_6 \cdot HCl$ C H N calculated(%) 69.35 6.65 2.31 found(%) 69.21 6.59 2.33

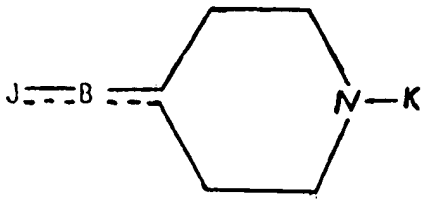
Table 10

Inhibitory effect against acetylcholinesterase in vitro					
Compound	Inhibitory activity on AChE $IC_{50}(\mu M)$	Compound	Inhibitory activity on AChE $IC_{50}(\mu M)$	Compound	Inhibitory activity on AChE $IC_{50}(\mu M)$
178	>10			226	0.0049
179	5.4	203	0.009	227	0.01
180	0.001	204	0.035	228	0.002
		205	0.014	229	0.04
182	0.8	206	0.41	230	0.16
		207	0.049	231	0.004
		208	0.062	232	0.1
185	0.00082	209	0.43	233	0.046
186	0.0015	210	0.06	234	0.0018
187	4.4	211	2	235	0.22
188	0.081	212	0.5	236	3.6
189	0.012	213	0.05	237	2.6
190	0.02	214	0.0084		
191	0.085	215	0.0042	239	0.18
192	0.013	216	0.017	240	0.0089
193	0.2	217	0.14	241	0.22
194	0.069	218	20	242	2.9
195	0.0071			243	4
196	0.0013			244	4.9
197	0.38	221	0.033		
198	0.0054	222	0.011		
199	0.023	223	0.0054		
		224	0.003		
		225	0.48	249	0.62

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

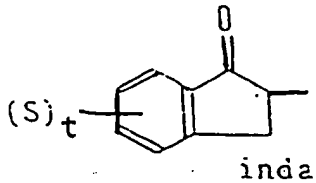
1. A cyclic amine compound having the following formula or a pharmacologically acceptable salt thereof:



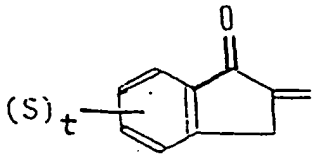
(XXV)

wherein:

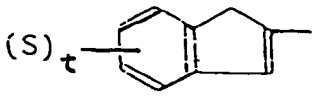
J is selected from:



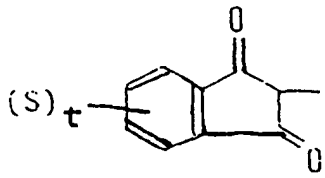
indanonyl



indanolidenyl



indenyl



indanedionyl

wherein S is a lower alkyl group having 1-6 carbon atoms, a lower alkoxy group having 1-6 carbon atoms, a halogen atom, a hydroxyl group, and t is 0-4, or $(S)_t$ may form a methylene dioxy group or an ethylene dioxy group on two adjacent carbon atoms of the phenyl group to which $(S)_t$ is attached;

B is one of the divalent groups $-(CHR^{22})_r-$, in which r is an integer from 0 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group; $=(CH-CH=CH)_b-$, in which b is an integer from 1 to 3; $=CH-(CH_2)_c-$, in which c is an integer from 0 to 9; or $=(CH-CH)_d=$, in which d is an integer from 0 to 5; and

K is a phenylalkyl group optionally substituted by a C_{1-6}alkyl group which may optionally be halogenated, a C_{1-6}alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6}alkoxycarbonyl group, an amino group, a C_{1-6}monoalkylamino group, a C_{1-6}dialkylamino group, a carbamoyl group, a C_{1-6}acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6}alkylaminocarbonyl group, a C_{1-6}alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6}alkoxy-C_{1-6}alkyl group; and

⎓ shows a single or a double bond.

2. A cyclic amine according to Claim 1 or a pharmacologically acceptable salt thereof, wherein B is $-(CHR^{22})_r-$; R^{22} is a hydrogen atom; and r is an integer of 1 to 10.

3. A cyclic amine compound as claimed in Claim 1 or a pharmacologically acceptable salt thereof, which is 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine.

4. A cyclic amine compound as claimed in Claim 1 or a pharmacologically acceptable salt thereof, which is 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methylpiperidine,

1-benzyl-4-[(5-methoxy-1-indanon)-2-yl] methylpiperidine,
1-benzyl-4-[(5,6-diethoxy-1-indanon)-2-yl] methylpiperidine,
1-benzyl-4-[(5,6-methylenedioxy-1-indanon)-2-yl] methylpiperidine,
1-(m-nitrobenzyl)-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine,
1-(m-fluorobenzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine,
1-benzyl-3-[(5,6-dimethoxy-1-indanon)-2-yl] propylpiperidine,
1-benzyl-4-[(5-isopropoxy-6-methoxy-1-indanon)-2-yl] methylpiperidine, or
1-benzyl-3-[(5,6-dimethoxy-1-indanolidenyl)-2-yl] propenylpiperidine.

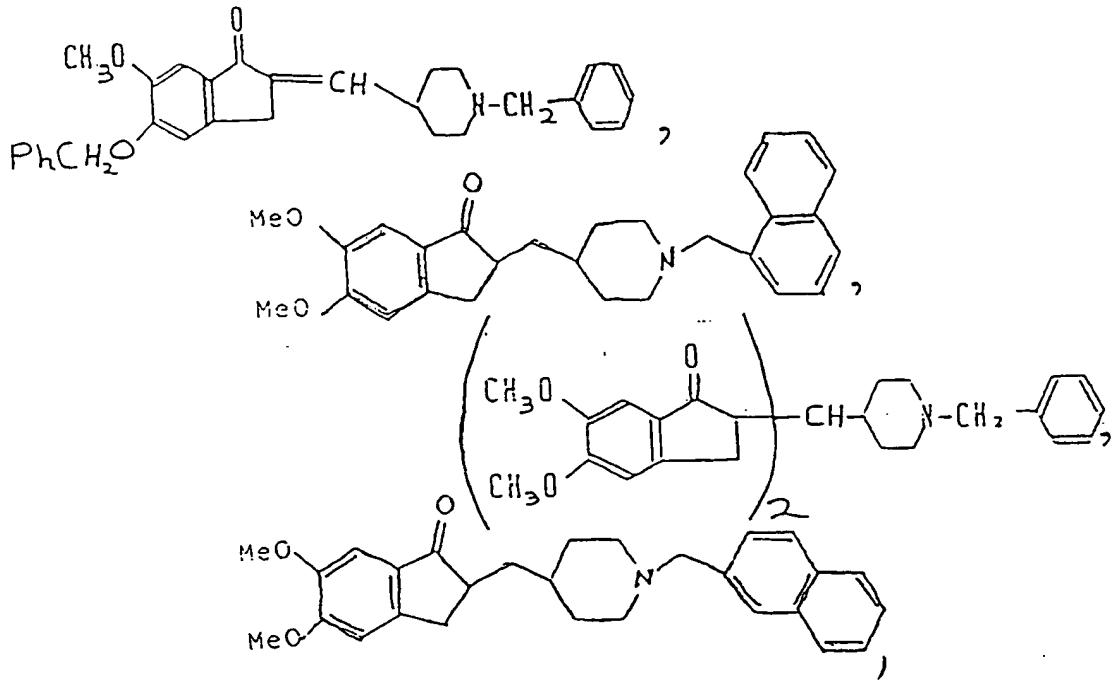
5. A therapeutical composition comprising a pharmacologically effective amount of a cyclic amine compound as defined in Claim 1 or a pharmacologically acceptable salt thereof, and a pharmacologically acceptable carrier.

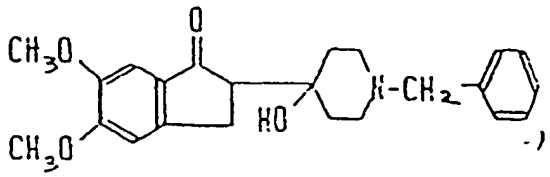
6. The use of a cyclic amine compound as defined in Claim 1 or a pharmacologically acceptable salt thereof for preparing a medicament for the treatment of a disease due to acetylcholinesterase activity.

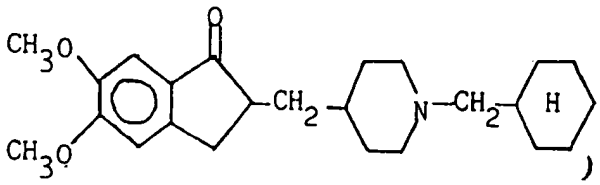
7. The use according to Claim 6, wherein the medicament is effective against senile dementia.

8. The use according to Claim 6, wherein the medicament is effective against senile dementia of the Alzheimer type.

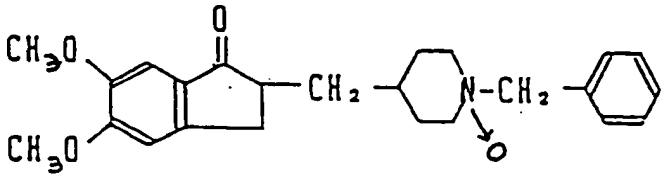
9. A cyclic amine compound or a pharmacologically acceptable salt thereof having the formula:







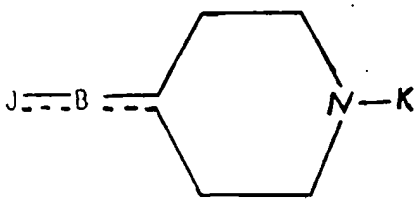
or



Claims for the following Contracting States : ES, GR

1. A process for preparing a pharmaceutical composition effective against a disease due to acetylcholinesterase activity comprising the step of mixing a pharmaceutically acceptable carrier and a cyclic amine compound having the fol-

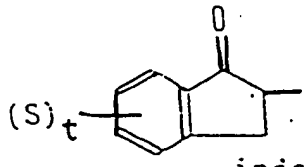
lowing formula or a pharmacologically acceptable salt thereof:



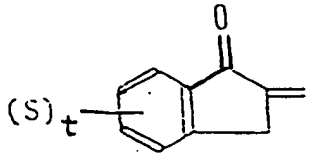
(XXV)

wherein:

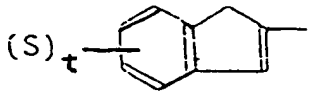
J is selected from:



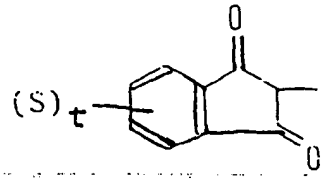
indanonyl



indanolidenyl



indenyl



indanedionyl

wherein S is a lower alkyl group having 1-6 carbon atoms, a lower alkoxy group having 1-6 carbon atoms, a halogen atom, a hydroxyl group, and t is 0-4, or $(S)_t$ may form a methylene dioxy group or an ethylene dioxy group on two adjacent carbon atoms of the phenyl group to which $(S)_t$ is attached;

B is one of the divalent groups $-(CHR^{22})_r-$, in which r is an integer from 0 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group; $=(CH-CH=CH)_b-$, in which b is an integer from 1 to 3; $=CH-(CH_2)_c-$, in which c is an integer from 0 to 9; $=(CH-CH)_d=$, in which d is an integer from 0 to 5; and

K is a phenylalkyl group optionally substituted by a C_{1-6}alkyl group which may optionally be halogenated, a C_{1-6}alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6}alkoxycarbonyl group,

an amino group, a C_{1-6}monoalkylamino group, a C_{1-6}dialkylamino group, a carbamoyl group, a C_{1-6}acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6}alkylaminocarbonyl group, a C_{1-6}alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6}alkoxy-C_{1-6}alkyl group; and

⋯ shows a single or a double bond.

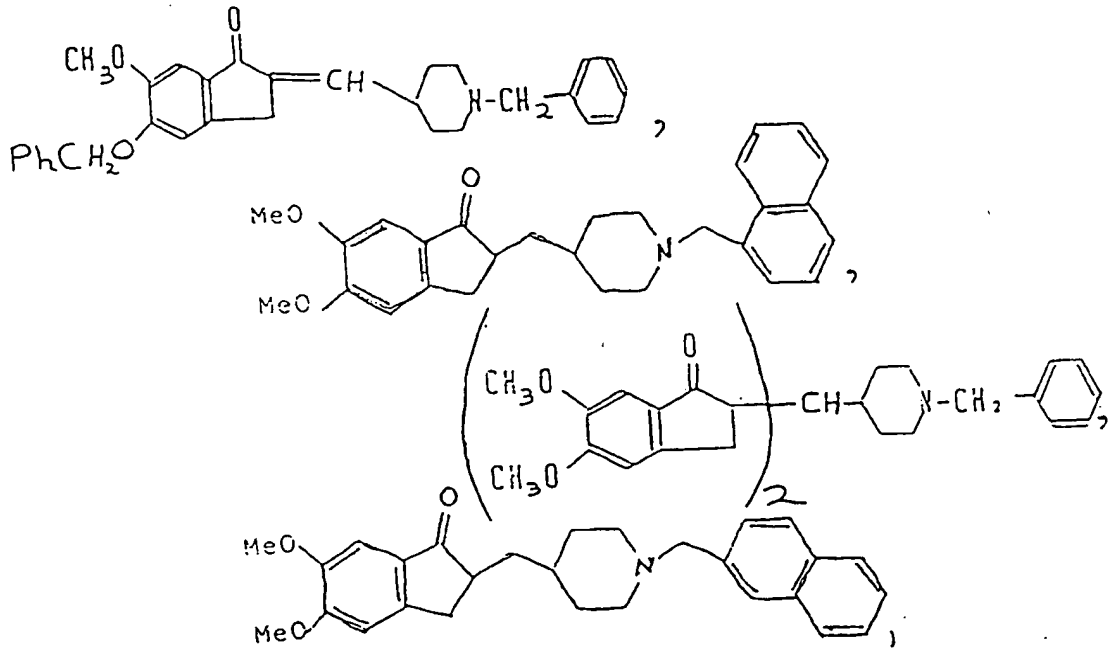
2. A process according to Claim 1, wherein B is $-(CHR^{22})_r-$; R^{22} is a hydrogen atom; and r is an integer of 1 to 10.

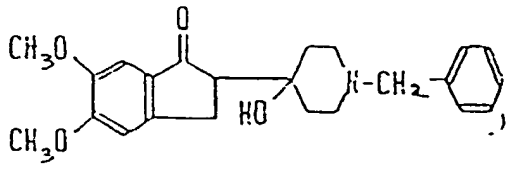
3. A process according to Claim 1, wherein the compound of formula XXV is 1-benzyl-4-[(5,6-dimethoxy -1-indanon)-2-yl] methylpiperidine .

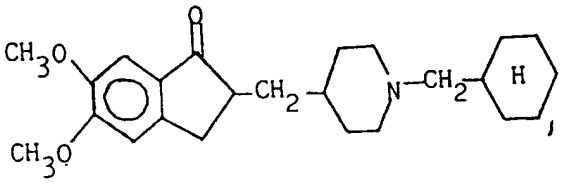
4. A process according to Claim 1, wherein the compound of formula XXV is
1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methylpiperidine,
1-benzyl-4-[(5-methoxy-1-indanon)-2-yl] methylpiperidine,
1-benzyl-4-[(5,6-diethoxy-1-indanon)-2-yl] methylpiperidine,
1-benzyl-4-[(5,6-methylenedioxy-1-indanon)-2-yl] methylpiperidine,
1-(m-nitrobenzyl)-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine,
1-(m-fluorobenzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methylpiperidine,
1-benzyl-3-[(5,6-dimethoxy-1-indanon)-2-yl] propylpiperidine,
1-benzyl-4-[(5-isopropoxy-6-methoxy-1-indanon)-2-yl] methylpiperidine, or
1-benzyl-3-[(5,6-dimethoxy-1-indanolidenyl)-2-yl] propenylpiperidine

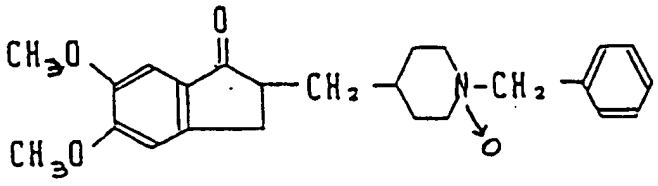
5. A process for preparing a pharmaceutical composition effective against a disease due to acetylcholinesterase activity comprising the step of mixing a pharmaceutically acceptable carrier and a cyclic amine compound or a pharmaco-

logically acceptable salt thereof having the formula:

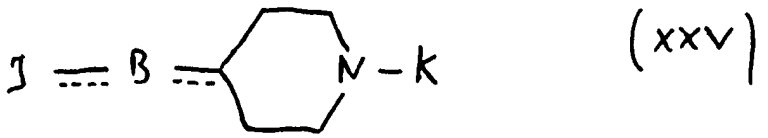








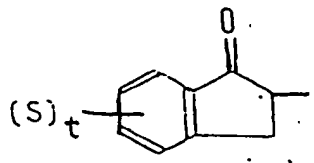
6. The use of a cyclic amine compound having the following formula or a pharmacologically acceptable salt thereof:



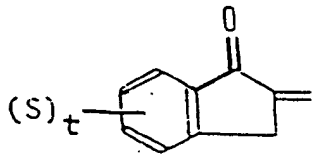
(xxv)

wherein:

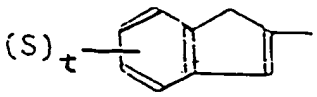
J is selected from:



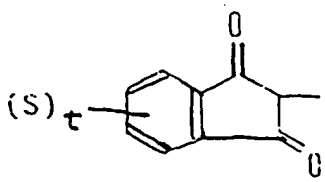
indanonyl



indanolidenyl



indenyl



indanedionyl

wherein S is a lower alkyl group having 1-6 carbon atoms, a lower alkoxy group having 1-6 carbon atoms, a halogen atom, a hydroxyl group, and t is 0-4, or $(S)_t$ may form a methylene dioxy group or an ethylene dioxy group on two adjacent carbon atoms of the phenyl group to which $(S)_t$ is attached;

B is one of the divalent groups $-(CHR^{22})_r-$, in which r is an integer from 0 to 10 and each R^{22} is independently either a hydrogen atom or a methyl group; $=(CH-CH=CH)_b-$, in which b is an integer from 1 to 3; $=CH-(CH_2)_c-$, in which c is an integer from 0 to 9; $=(CH-CH)_d=$, in which d is an integer from 0 to 5; $-CO-CH=CH-CH_2-$; $-CO-CH_2-CH(OH)-CH_2-$; $-CH(CH_3)-CO-NH-CH_2-$; $-CH=CH-CO-NH-(CH_2)_2-$; -NH-; -O-; or -S-;

and

K is a phenylalkyl group optionally substituted by a C_{1-6}alkyl group which may optionally be halogenated, a C_{1-6}alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6}alkoxycarbonyl group, an amino group, a C_{1-6}monoalkylamino group, a C_{1-6}dialkylamino group, a carbamoyl group, a C_{1-6}acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6}alkylaminocarbonyl group, a C_{1-6}alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6}alkoxy-C_{1-6}alkyl group; and

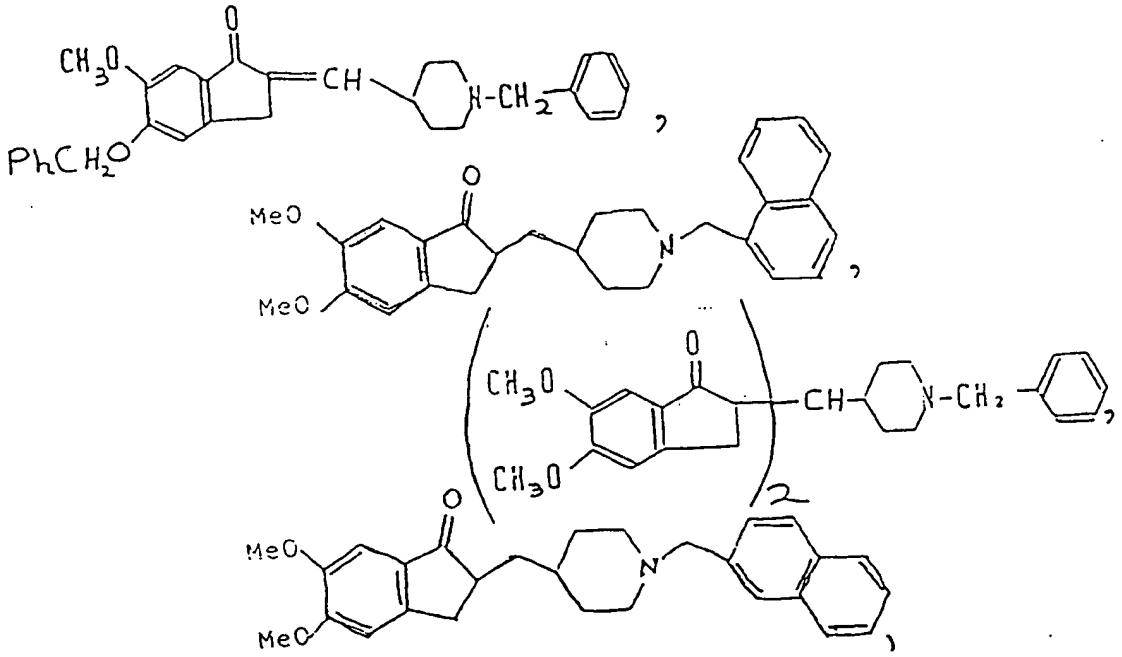
⋯ shows a single or a double bond.

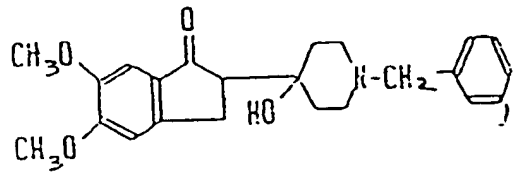
for the manufacture of a medicament for the treatment of a disease due to acetylcholinesterase activity.

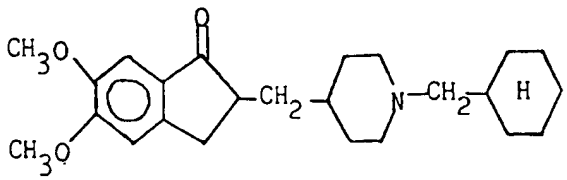
7. The use according to Claim 6, wherein the medicament is effective against senile dementia.

8. The use according to Claim 6, wherein the medicament is effective against senile dementia of the Alzheimer type.

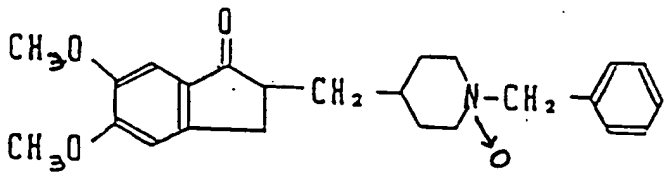
9. The use of a cyclic amine compound or a pharmacologically acceptable salt thereof having the formula:







or

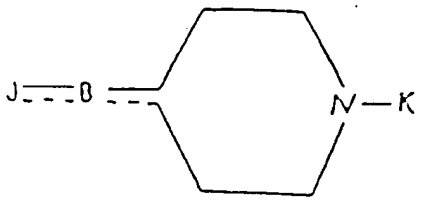


for the manufacture of a medicament for the treatment of a disease due to acetylcholinesterase activity.

Patentansprüche

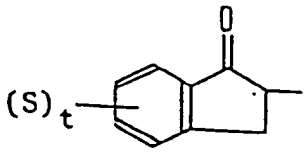
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Cyclische Aminverbindung mit der folgenden Formel oder deren pharmakologisch annehmbare Salze:

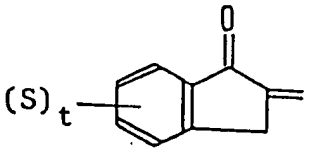


(XXV)

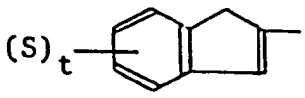
worin J ausgewählt wird aus:



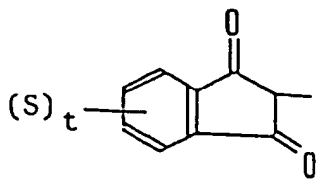
Indanonyl



Indanolidenyl



Indenyl



Indandionyl

worin S eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Niederalkoxygruppe mit 1 bis 6 Kohlenstoffatomen, ein Halogenatom oder eine Hydroxylgruppe ist, und t 0 bis 4 ist, oder $(S)_t$ eine Methylendioxygruppe oder eine Ethylendioxygruppe an zwei benachbarten Kohlenstoffatomen der Phenylgruppe bilden kann, an die $(S)_t$ gebunden ist;

B eine der zweiwertigen Gruppen $-(CHR^{22})_r-$, wobei r eine ganze Zahl von 0 bis 10 ist und jedes R^{22} unabhängig entweder ein Wasserstoffatom oder eine Methylgruppe ist; $=(CH-CH=CH)_b-$, worin b eine ganze Zahl von 1 bis 3 ist; $=CH-(CH_2)_c-$, worin c eine ganze Zahl von 0 bis 9 ist; oder $=(CH-CH)_d=$, worin d eine ganze Zahl von 0 bis 5 ist, darstellt; und

K darstellt: eine Phenylalkylgruppe, gegebenenfalls substituiert mit einer C_{1-6}-Alkylgruppe, welche gegebenenfalls halogeniert sein kann, einer C_{1-6}-Alkoxygruppe, einer Nitrogruppe, einem Halogenatom, einer Carboxylgruppe, einer Benzyloxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminogruppe, einer C_{1-6}-Monoalkylaminogruppe, einer C_{1-6}-Dialkylaminogruppe, einer Carbamoylgruppe, einer C_{1-6}-Acylaminogruppe, einer Cyclohexyloxycarbonylgruppe, einer C_{1-6}-Alkylaminocarbonylgruppe, einer C_{1-6}-Alkylcarbonyloxygruppe, einer Hydroxylgruppe, einer Formylgruppe oder einer C_{1-6}-Alkoxy-C_{1-6}-alkylgruppe; und

⎓ eine Einfach- oder Doppelbindung bedeutet.

2. Cyclisches Amin gemäss Anspruch 1 oder ein pharmakologisch annehmbares Salz davon, worin B $-(CHR^{22})_r-$ ist; R^{22} ein Wasserstoffatom ist und r eine ganze Zahl von 1 bis 10 ist.

3. Cyclische Aminverbindung gemäss Anspruch 1, welche 1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidin ist, oder eines ihrer pharmakologisch annehmbaren Salze.

4. Cyclische Aminverbindung gemäss Anspruch 1, welche 1-Benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidin, 1-Benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidin, 1-Benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidin, 1-Benzyl-4-((5,6-methylendioxy-1-indanon)-2-yl)methylpiperidin, 1-(m-Nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidin, 1-(m-Fluorbenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidin, 1-Benzyl-3-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidin, 1-Benzyl-4-((5,6-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidin oder 1-Benzyl-3-((5,6-dimethoxy-1-indanolidenyl)-2-yl)propenylpiperidin ist, oder eines ihrer pharmakologisch annehmbaren Salze.

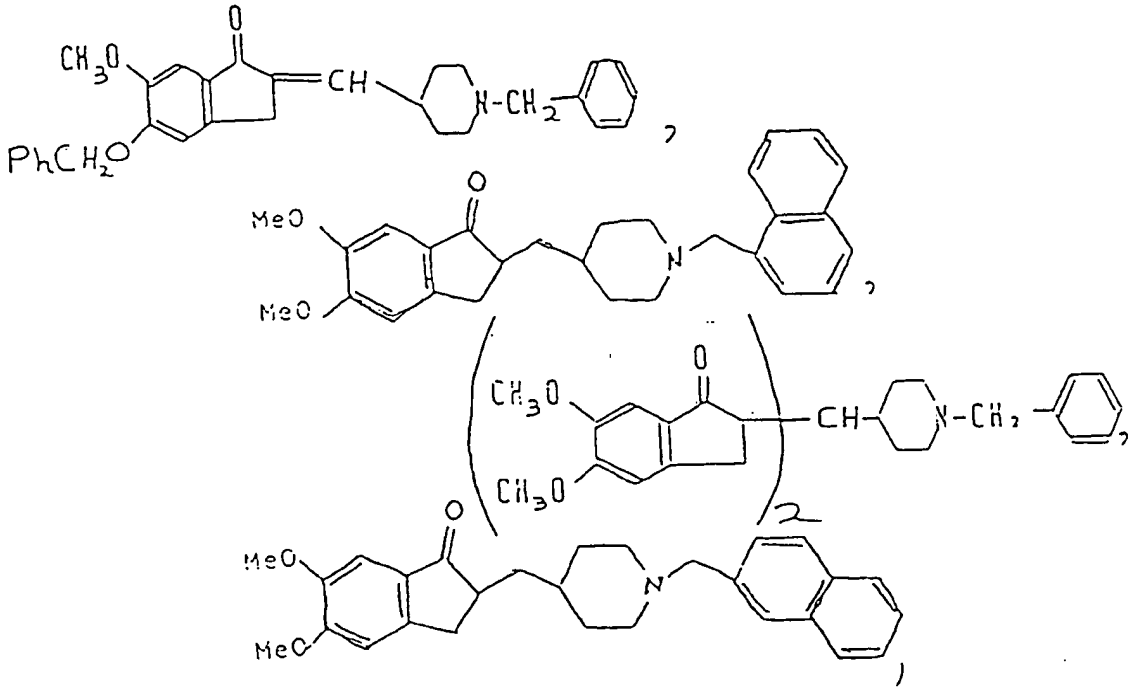
5. Therapeutische Zusammensetzung, umfassend eine pharmakologisch wirksame Menge einer cyclischen Aminverbindung gemäss Anspruch 1 oder eines ihrer pharmakologisch annehmbaren Salze, und einen pharmakologisch annehmbaren Träger.

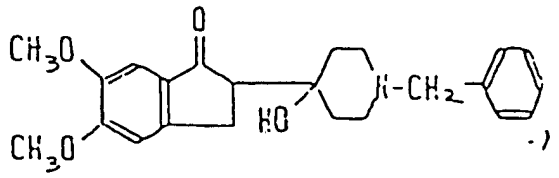
6. Verwendung einer cyclischen Aminverbindung gemäss Anspruch 1 oder eines ihrer pharmakologisch annehmbaren Salze zur Herstellung eines Arzneimittels zur Behandlung einer Krankheit aufgrund von Acetylcholinesteraseaktivität.

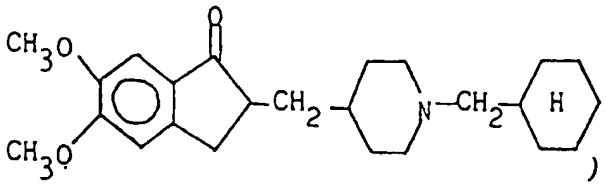
7. Verwendung gemäss Anspruch 6, wobei das Medikament wirksam ist gegen die senile Demenz.

8. Verwendung gemäss Anspruch 6, wobei das Medikament wirksam ist gegen die Alzheimer'sche senile Demenz.

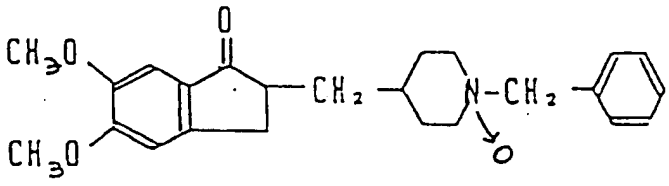
9. Cyclische Aminverbindung oder eines ihrer pharmakologisch annehmbaren Salze mit der Formel





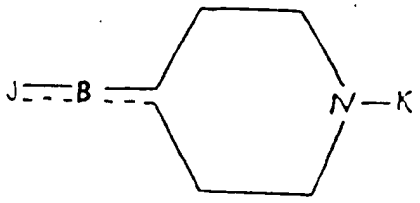


oder



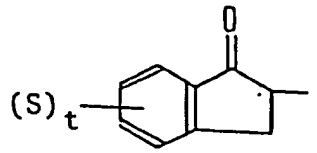
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welche wirksam ist gegen eine Krankheit aufgrund von Acetylcholinesteraseaktivität, umfassend den Schritt der Mischung eines pharmazeutisch annehmbaren Trägers und einer cyclischen Aminverbindung mit der folgenden Formel oder eines ihrer pharmakologisch annehmbaren Salze:

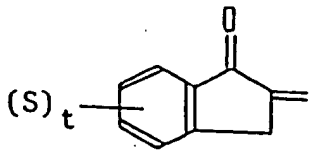


(XXV)

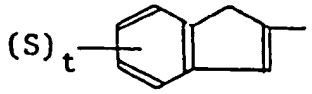
worin J ausgewählt wird aus:



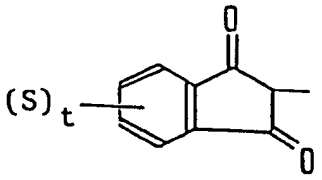
Indanonyl



Indanolidenyl



Indenyl



Indandionyl

worin S eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Niederalkoxygruppe mit 1 bis 6 Kohlenstoffatomen, ein Halogenatom oder eine Hydroxylgruppe ist, und t 0 bis 4 ist, oder $(S)_t$ eine Methylendioxygruppe oder eine Ethylendioxygruppe an zwei benachbarten Kohlenstoffatomen der Phenylgruppe bilden kann, an die $(S)_t$ gebunden ist;
B eine der zweiwertigen Gruppen $-(CHR^{22})_r-$, wobei r eine ganze Zahl von 0 bis 10 ist und jedes R^{22} unabhängig entweder ein Wasserstoffatom oder eine Methylgruppe ist; $=(CH-CH=CH)_b-$, worin b eine ganze Zahl von 1 bis 3 ist; $=CH-(CH_2)_c-$, worin c eine ganze Zahl von 0 bis 9 ist; oder $=(CH-CH)_d=$, worin d eine ganze Zahl von 0 bis 5 ist, darstellt; und
K darstellt: eine Phenylalkylgruppe, gegebenenfalls substituiert mit einer C_{1-6}-Alkylgruppe, welche gegebenenfalls halogeniert sein kann, einer C_{1-6}-Alkoxygruppe, einer Nitrogruppe, einem Halogenatom, einer Carboxylgruppe, einer Benzyloxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminogruppe, einer C_{1-6}-Monoalkylaminogruppe, einer C_{1-6}-Dialkylaminogruppe, einer Carbamoylgruppe, einer C_{1-6}-Acylaminogruppe, einer Cyclohexyloxycarbonylgruppe, einer C_{1-6}-Alkylaminocarbonylgruppe, einer C_{1-6}-Alkylcarbonyloxygruppe, einer Hydroxylgruppe, einer Formylgruppe oder einer C_{1-6}-Alkoxy-C_{1-6}-alkylgruppe; und
⎓ eine Einfach- oder Doppelbindung bedeutet.

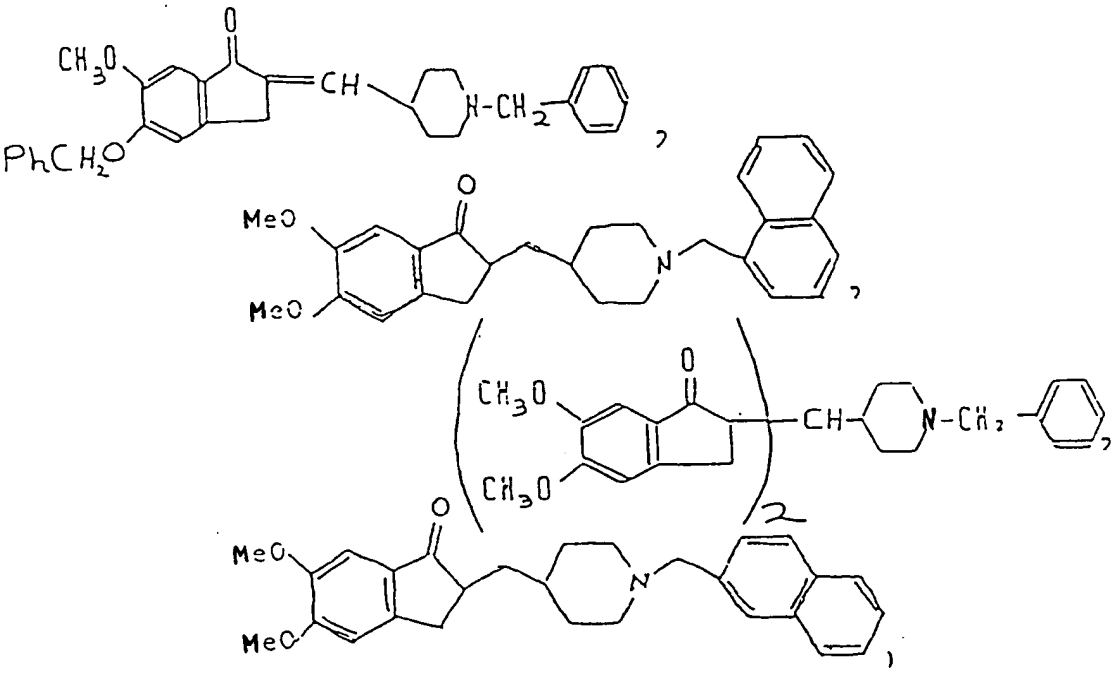
2. Verfahren gemäss Anspruch 1, worin B $-(CHR^{22})_r-$ ist; R^{22} ein Wasserstoffatom ist und r eine ganze Zahl von 1 bis 10 ist.

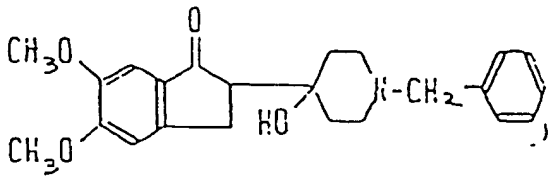
3. Verfahren gemäss Anspruch 1, worin die Verbindung der Formel (XXV) 1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidin ist.

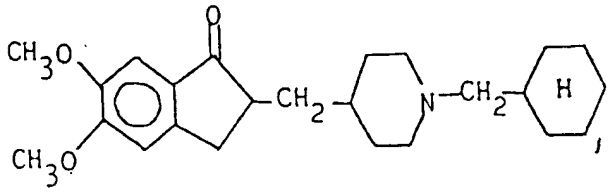
4. Verfahren gemäss Anspruch 1, worin die Verbindung der Formel (XXV)
1-Benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidin,
1-Benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidin,
1-Benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidin,

1-Benzyl-4-((5,6-methylendioxy-1-indanon)-2-yl)methylpiperidin,
1-(m-Nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidin,
1-(m-Fluorbenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidin,
1-Benzyl-3-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidin,
1-Benzyl-4-((5,6-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidin oder
1-Benzyl-3-((5,6-dimethoxy-1-indanolidenyl)-2-yl)propenylpiperidin
ist.

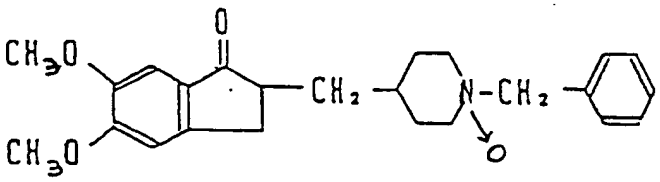
5. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welche wirksam gegen eine Krankheit aufgrund von Acetylcholinesteraseaktivität ist, umfassend den Schritt der Mischung eines pharmazeutisch annehmbaren Trägers und einer cyclischen Aminverbindung oder eines pharmakologisch annehmbaren Salzes davon mit der Formel:



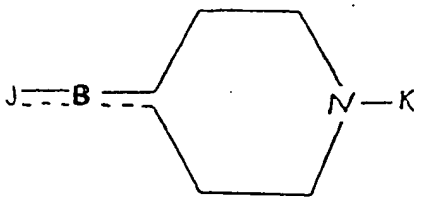




oder

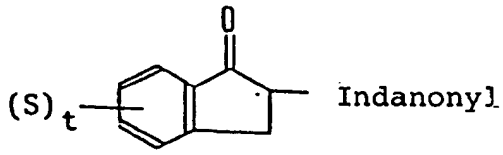


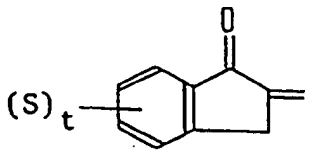
6. Verwendung einer cyclischen Aminverbindung mit der folgenden Formel oder eines pharmakologisch annehmbaren Salzes davon:



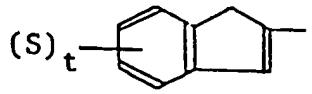
(XXV)

worin J ausgewählt wird aus:

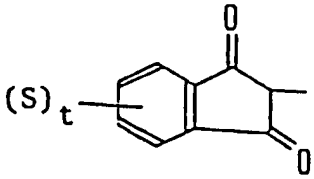




Indanolidenyl



Indenyl



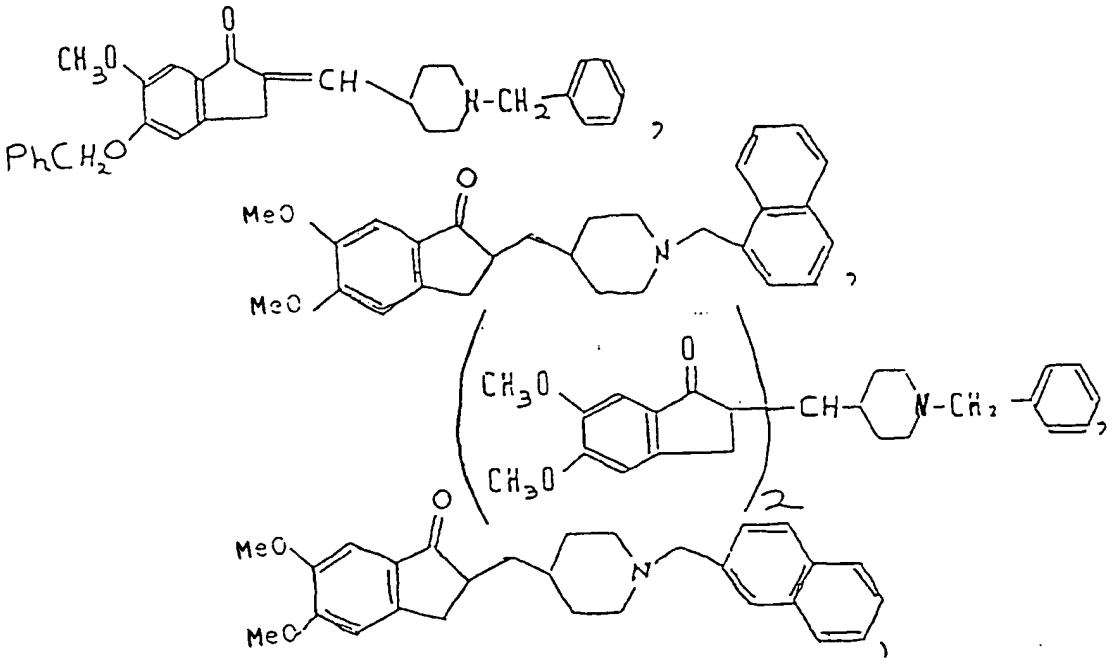
Indandionyl

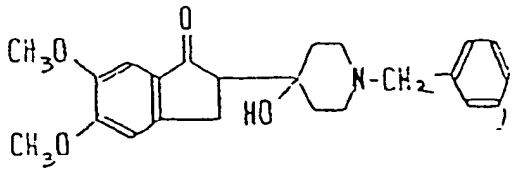
worin S eine Niederalkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Niederalkoxygruppe mit 1 bis 6 Kohlenstoffatomen, ein Halogenatom oder eine Hydroxylgruppe ist, und t 0 bis 4 ist, oder $(S)_t$ eine Methylendioxygruppe oder eine Ethylendioxygruppe an zwei benachbarten Kohlenstoffatomen der Phenylgruppe, an die $(S)_t$ gebunden ist, bilden kann;
B eine der folgenden zweiwertigen Gruppen ist: $-(CHR^{22})_r-$, wobei r eine ganze Zahl von 0 bis 10 ist und jedes R^{22} unabhängig entweder ein Wasserstoffatom oder eine Methylgruppe ist; $=(CH-CH=CH)_b-$, worin b eine ganze Zahl von 1 bis 3 ist; $=CH-(CH_2)_c-$, worin c eine ganze Zahl von 0 bis 9 ist; oder $=(CH-CH)_d=$, worin d eine ganze Zahl von 0 bis 5 ist; $-CO-CH=CH-CH_2-$; $-CO-CH_2-CH(OH)-CH_2-$;
$-CH(CH_3)-CO-NH-CH_2-$; $-CH=CH-CO-NH-(CH_2)_2-$; -NH-; -O- oder -S-;
und
K eine Phenylalkylgruppe ist, welche gegebenenfalls substituiert ist mit einer C_{1-6}-Alkylgruppe, die gegebenenfalls halogeniert sein kann, einer C_{1-6}-Alkoxygruppe, einer Nitrogruppe, einem Halogenatom, einer Carboxylgruppe, einer Benzyloxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer Aminogruppe, einer C_{1-6}-Monoalkylaminogruppe, einer C_{1-6}-Dialkylaminogruppe, einer Carbamoylgruppe, einer C_{1-6}-Acylaminogruppe, einer Cyclohexyloxycarbonylgruppe, einer C_{1-6}-Alkylaminocarbonylgruppe, einer C_{1-6}-Alkylcarbonyloxygruppe, einer Hydroxylgruppe, einer Formylgruppe oder einer C_{1-6}-Alkoxy-C_{1-6}-alkylgruppe; und
⎓ eine Einfach- oder Doppelbindung bedeutet,
zur Herstellung eines Arzneimittels zur Behandlung einer Krankheit aufgrund von Acetylcholinesteraseaktivität.

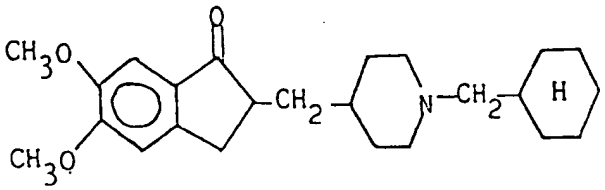
7. Verwendung gemäss Anspruch 6, wobei das Medikament wirksam ist gegen senile Demenz.

8. Verwendung gemäss Anspruch 6, wobei das Medikament wirksam ist gegen die Alzheimer'sche senile Demenz.

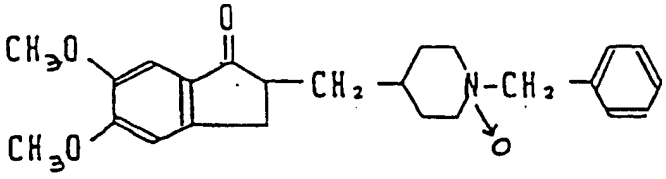
9. Verwendung einer cyclischen Aminverbindung oder eines ihrer pharmakologisch annehmbaren Salze mit der Formel







oder

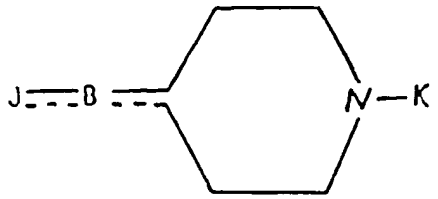


zur Herstellung eines Arzneimittels zur Behandlung einer Krankheit aufgrund von Acetylcholinesteraseaktivität.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

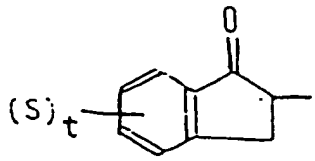
1. Amine cyclique répondant à la formule suivante, ou sel pharmacologiquement acceptable de celle-ci :



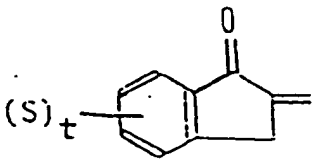
(XXV)

où :

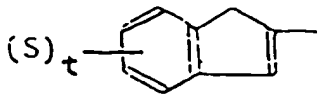
J est choisi parmi :



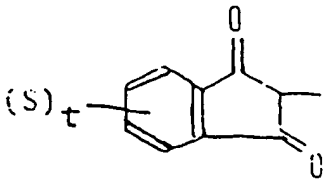
indanonyle



indanolidényle



indényle



indanedionyle

où S est un groupe alkyle inférieur ayant 1 à 6 atomes de carbone, un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone, un atome d'halogène ou un groupe hydroxy et t est 0 à 4, ou $(S)_t$ peut former un groupe méthylènedioxy ou un groupe éthylènedioxy sur deux atomes de carbone adjacents du groupe phényle auquel $(S)_t$ est fixé ;

B est un des groupes divalents $-(CHR^{22})_r-$, où r est un entier de 0 à 10 et chaque R^{22} est indépendamment soit un atome d'hydrogène soit un groupe méthyle ; $=(CH-CH=CH)_b-$, où b est un entier de 1 à 3 ; $=CH-(CH_2)_c-$, où c est un entier de 0 à 9 ; ou $=(CH-CH)_d=$, où d est un entier de 0 à 5 ; et

K est un groupe phénylalkyle, éventuellement substitué par un groupe alkyle en C_{1-6} qui peut éventuellement être halogéné, un groupe alcoxy en C_{1-6}, un groupe nitro, un atome d'halogène, un groupe carboxy, un groupe benzyloxy, un groupe (alcoxy en C_{1-6}) carbonyle, un groupe amino, un groupe monoalkylamino en C_{1-6}, un groupe di(alkyl en C_{1-6})amino, un groupe carbamoyle, un groupe acylamino en C_{1-6}, un groupe cyclohexyloxycarbonyle,

un groupe (alkyl en C_{1-6})aminocarbonyle, un groupe (alkyl en C_{1-6})carbonyloxy, un groupe hydroxy, un groupe formyle ou un groupe (alcoxy en C_{1-6}) alkyle en C_{1-6} ; et

⋯ représente une simple liaison ou une double liaison.

2. Amine cyclique selon la revendication 1 ou sel pharmacologiquement acceptable de celle-ci, où B est $-(CHR^{22})_r-$; R^{22} est un atome d'hydrogène ; et r est un entier de 1 à 10.

3. Amine cyclique selon la revendication 1 ou sel pharmacologiquement acceptable de celle-ci, qui est la 1-benzyl-4-[(5,6-diméthoxy-1-indanone)-2-yl]méthylpipéridine.

4. Amine cyclique selon la revendication 1 ou sel pharmacologiquement acceptable de celle-ci, qui est
la 1-benzyl-4-[(5,6-diméthoxy-1-indanone)-2-ylidényl]méthylpipéridine,
la 1-benzyl-4-[(5-méthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-benzyl-4-[(5,6-diéthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-benzyl-4-[(5,6-méthylènedioxy-1-indanone)-2-yl]méthylpipéridine,
la 1-(m-nitrobenzyl)-4-[(5,6-diméthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-(m-fluorobenzyl)-4-[(5,6-diméthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-benzyl-3-[(5,6-diméthoxy-1-indanone)-2-yl]propylpipéridine,
la 1-benzyl-4-[(5-isopropoxy-6-méthoxy-1-indanone)-2-yl]méthylpipéridine ou
la 1-benzyl-3-[(5,6-diméthoxy-1-indanolidényl)-2-yl]propénylpipéridine.

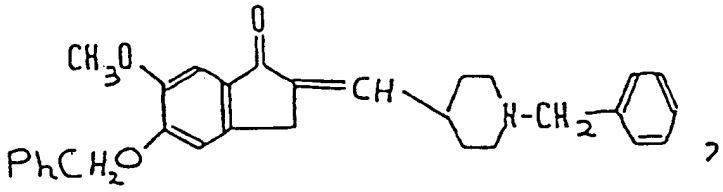
5. Composition thérapeutique comprenant une quantité pharmacologiquement efficace d'une amine cyclique telle que définie dans la revendication 1 ou d'un sel pharmacologiquement acceptable de celle-ci et un véhicule pharmacologiquement acceptable.

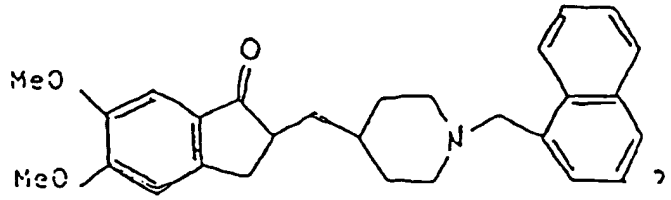
6. Utilisation d'une amine cyclique telle que définie dans la revendication 1 ou d'un sel pharmacologiquement acceptable de celle-ci pour la préparation d'un médicament pour le traitement d'une maladie due à l'activité de l'acétylcholinestérase.

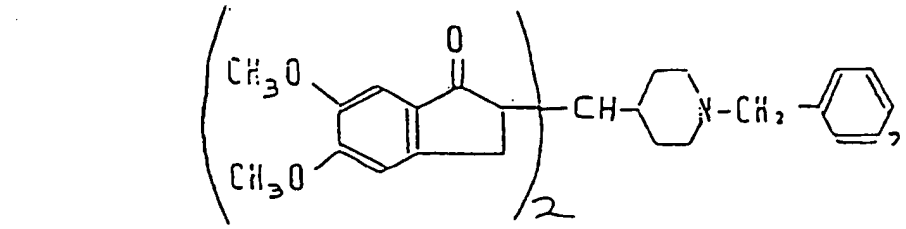
7. Utilisation selon la revendication 6, dans laquelle le médicament est efficace contre la démence sénile.

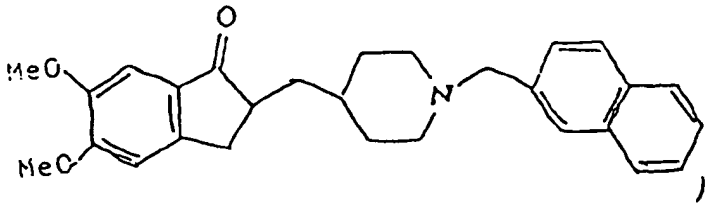
8. Utilisation selon la revendication 6, dans laquelle le médicament est efficace contre la démence sénile de type Alzheimer.

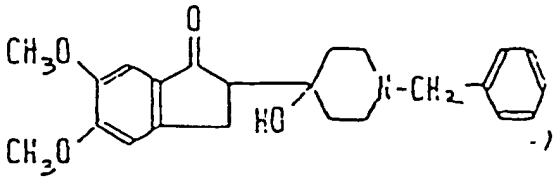
9. Amine cyclique ou sel pharmacologiquement acceptable de celle-ci répondant à la formule :

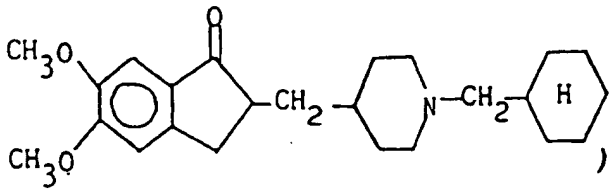




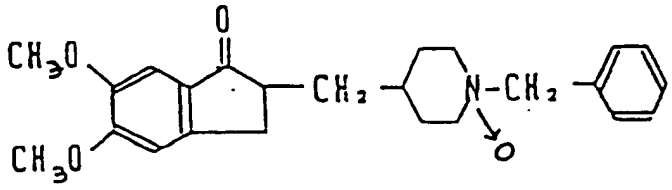








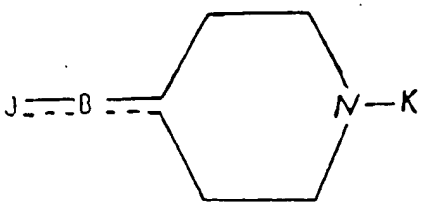
ou



Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour préparer une composition pharmaceutique efficace contre une maladie due à l'activité de l'acétylcholinestérase, comprenant l'étape de mélange d'un véhicule pharmaceutiquement acceptable et d'une amine cyclique

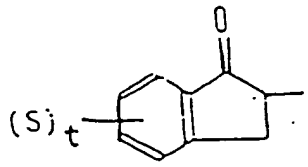
répondant à la formule suivante, ou d'un sel pharmacologiquement acceptable de celle-ci :



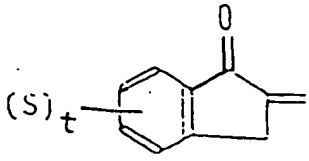
(XXV)

où :

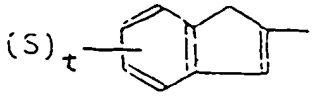
J est choisi parmi :



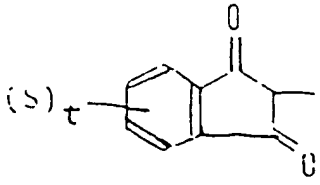
indanonyle



indanolidényle



indényle



indanedionyle

où S est un groupe alkyle inférieur ayant 1 à 6 atomes de carbone, un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone, un atome d'halogène ou un groupe hydroxy et t est 0 à 4, ou $(S)_t$ peut former un groupe méthylènedioxy ou un groupe éthylènedioxy sur deux atomes de carbone adjacents du groupe phényle auquel $(S)_t$ est fixé ;

B est un des groupes divalents $-(CHR^{22})_r-$, où r est un entier de 0 à 10 et chaque R^{22} est indépendamment soit un atome d'hydrogène soit un groupe méthyle ; $=(CH-CH=CH)_b-$, où b est un entier de 1 à 3 ; $=CH-(CH_2)_c-$, où c est un entier de 0 à 9 ; ou $=(CH-CH)_d=$, où d est un entier de 0 à 5 ; et

K est un groupe phénylalkyle, éventuellement substitué par un groupe alkyle en C_{1-6} qui peut éventuellement être halogéné, un groupe alcoxy en C_{1-6}, un groupe nitro, un atome d'halogène, un groupe carboxy, un groupe benzyloxy, un groupe (alcoxy en C_{1-6}) carbonyle, un groupe amino, un groupe monoalkylamino en C_{1-6}, un groupe di(alkyl en C_{1-6})amino, un groupe carbamoyle, un groupe acylamino en C_{1-6}, un groupe cyclohexyloxycarbonyle, un groupe (alkyl en C_{1-6})aminocarbonyle, un groupe (alkyl en C_{1-6})carbonyloxy, un groupe hydroxy, un groupe formyle ou un groupe (alcoxy en C_{1-6}) alkyle en C_{1-6} ; et

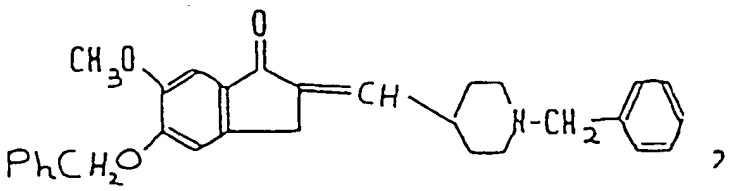
⎓ représente une simple liaison ou une double liaison.

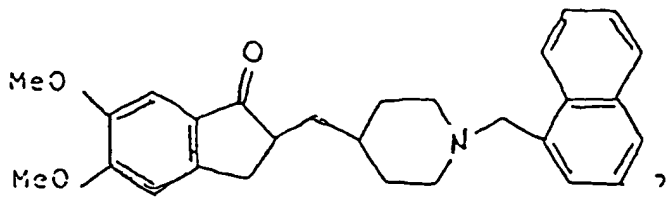
2. Procédé selon la revendication 1 où B est $-(CHR^{22})_r-$; R^{22} est un atome d'hydrogène ; et r est un entier de 1 à 10.

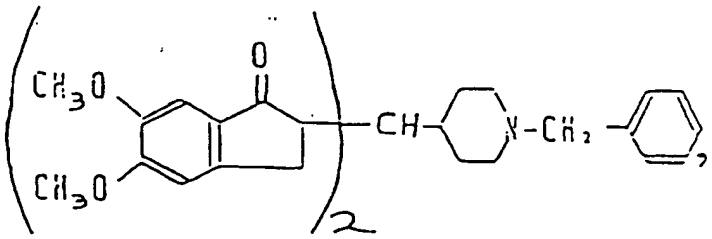
3. Procédé selon la revendication 1, où le composé de formule XXV est la 1-benzyl-4-[(5,6-diméthoxy-1-indanone)-2-yl]méthylpipéridine.

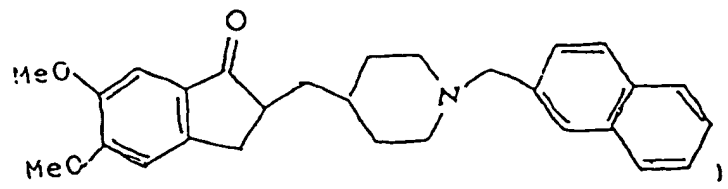
4. Procédé selon la revendication 1, où le composé de formule XXV est
la 1-benzyl-4-[(5,6-diméthoxy-1-indanone)-2-ylidényl]méthylpipéridine,
la 1-benzyl-4-[(5-méthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-benzyl-4-[(5,6-diéthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-benzyl-4-[(5,6-méthylènedioxy-1-indanone)-2-yl]méthylpipéridine,
la 1-(m-nitrobenzyl)-4-[(5,6-diméthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-(m-fluorobenzyl)-4-[(5,6-diméthoxy-1-indanone)-2-yl]méthylpipéridine,
la 1-benzyl-3-[(5,6-diméthoxy-1-indanone)-2-yl]propylpipéridine,
la 1-benzyl-4-[(5-isopropoxy-6-méthoxy-1-indanone)-2-yl]méthylpipéridine ou
la 1-benzyl-3-[(5,6-diméthoxy-1-indanolidényl)-2-yl]propénylpipéridine.

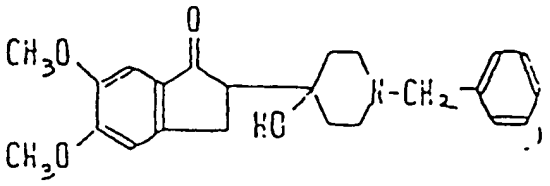
5. Procédé pour préparer une composition pharmaceutique efficace contre une maladie due à l'activité de l'acétylcholinestérase, comprenant l'étape de mélange d'un véhicule pharmaceutiquement acceptable et d'une amine cyclique ou d'un sel pharmacologiquement acceptable de celle-ci répondant à la formule :

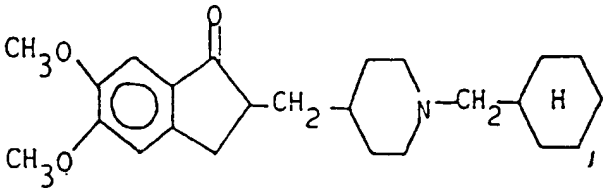




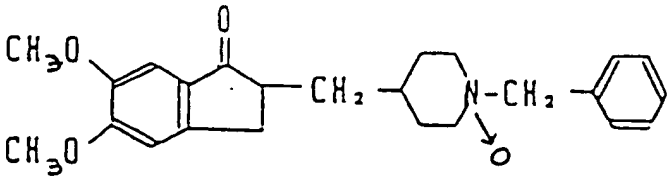




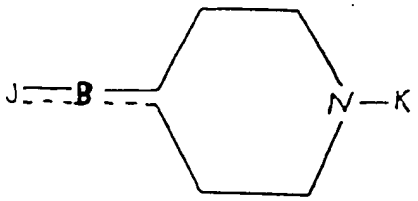




ou



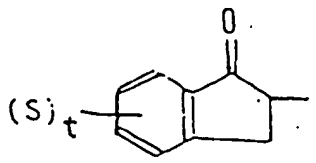
6. Utilisation d'une amine cyclique répondant à la formule suivante ou d'un sel pharmacologiquement acceptable de celle-ci :



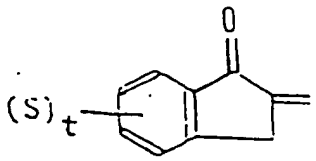
(XXV)

où :

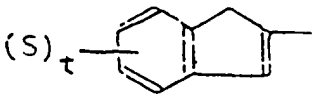
J est choisi parmi :



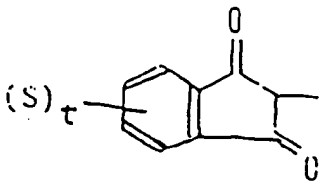
indanonyle



indanolidényle



indényle



indanedionyle

où S est un groupe alkyle inférieur ayant 1 à 6 atomes de carbone, un groupe alcoxy inférieur ayant 1 à 6 atomes de carbone, un atome d'halogène ou un groupe hydroxy et t est 0 à 4, ou $(S)_t$ peut former un groupe méthylènedioxy ou un groupe éthylènedioxy sur deux atomes de carbone adjacents du groupe phényle auquel $(S)_t$ est fixé ;

B est un des groupes divalents $-(CHR^{22})_r-$, où r est un entier de 0 à 10 et chaque R^{22} est indépendamment soit un atome d'hydrogène soit un groupe méthyle ; $=(CH-CH=CH)_b-$, où b est un entier de 1 à 3 ; $=CH-(CH_2)_c-$, où c est un entier de 0 à 9 ; ou $=(CH-CH)_d=$, où d est un entier de 0 à 5 ; $-CO-CH=CH-CH_2-$; $-CO-CH_2-CH(OH)-CH_2-$; $-CH(CH_3)-CO-NH-CH_2-$; $-CH=CH-CO-NH-(CH_2)_2-$; -NH- ; -O- ; ou -S- ; et

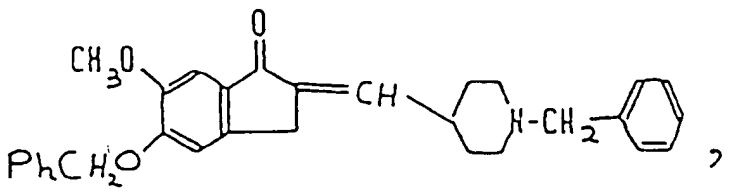
K est un groupe phénylalkyle, éventuellement substitué par un groupe alkyle en C_{1-6} qui peut éventuellement être halogéné, un groupe alcoxy en C_{1-6}, un groupe nitro, un atome d'halogène, un groupe carboxy, un groupe benzyloxy, un groupe (alcoxy en C_{1-6}) carbonyle, un groupe amino, un groupe monoalkylamino en C_{1-6}, un groupe di(alkyl en C_{1-6})amino, un groupe carbamoyle, un groupe acylamino en C_{1-6}, un groupe cyclohexyloxycarbonyle, un groupe (alkyl en C_{1-6})aminocarbonyle, un groupe (alkyl en C_{1-6})carbonyloxy, un groupe hydroxy, un groupe formyle ou un groupe (alcoxy en C_{1-6}) alkyle en C_{1-6} ; et

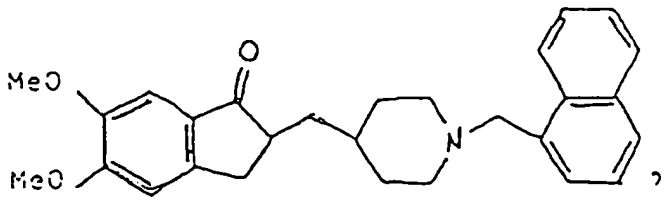
⎓ représente une simple liaison ou une double liaison, pour la préparation d'un médicament pour le traitement d'une maladie due à l'activité de l'acétylcholinestérase.

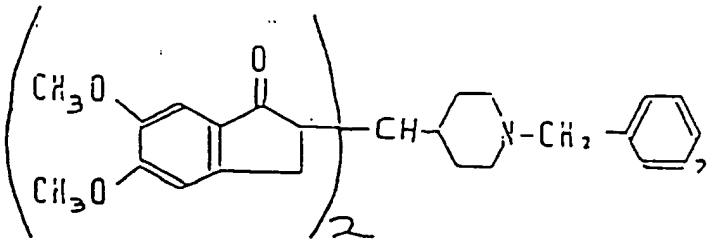
7. Utilisation selon la revendication 6, dans laquelle le médicament est efficace contre la démence sénile.

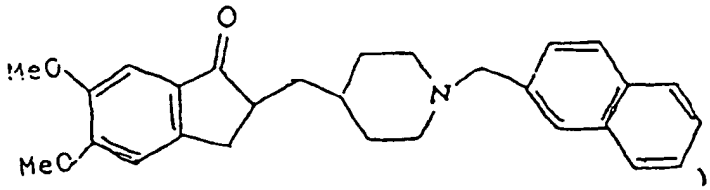
8. Utilisation selon la revendication 6, dans laquelle le médicament est efficace contre la démence sénile de type Alzheimer.

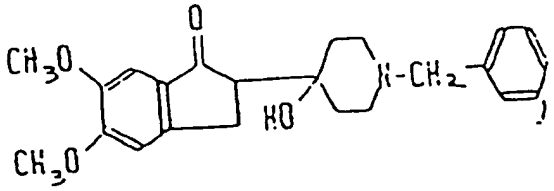
9. Utilisation d'une amine cyclique ou d'un sel pharmacologiquement acceptable de celle-ci répondant à la formule :

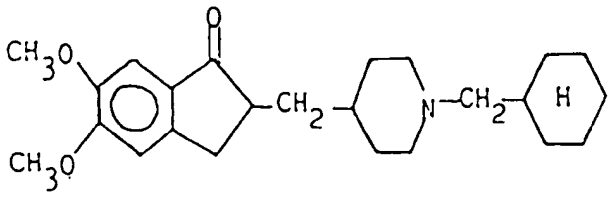












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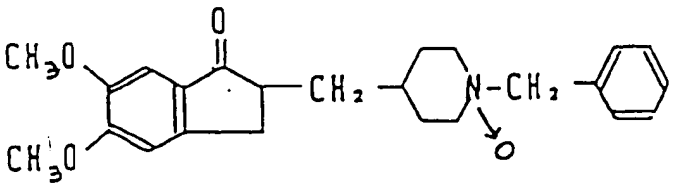

pour la préparation d'un médicament pour le traitement d'une maladie due à l'activité de l'acétylcholinestérase.